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Original Communications

THE EFFECT OF LOCAL HYPOTHERMIA ON THE GASTRIC SECRETORY MECHANISMS OF THE ANTRUM

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THE role of the antrum in gastric secretion has fascinated and perplexed physiologists and surgeons since Edkins[2] (1906) first proposed a gastric stimulating hormone (gastrin) on the basis of finding a stimulant in pyloric mucosal extracts. A voluminous amount of research by a number of investigators[1, 3-6, 8, 9] has succeeded in demonstrating the following facts concerning the antral phase of gastric secretion: (1) The stimulatory mechanism is hormonal with activation via chemical excitants and also through the agency of mechanical distention. (2) Inhibition of gastric secretion can be elicited by certain agents in contact with the antral mucosa, that is, acid, atropine, and local anesthetics.

In the course of studies in this clinic on the effect of local gastric cooling on the physiologic functions of the stomach, it was observed that the digestive power of gastric juice is suspended completely by temperatures of 15° C. or lower. It was found also that the secretion of gastric juice was markedly decreased by local hypothermia, an effect which is due in part probably to a decrease in blood flow during the cold state.[7] It was believed worthwhile ascertaining whether local hypothermia produced any alteration in the antral phase of gastric secretion.

MATERIALS AND METHODS

Adult mongrel dogs, weighing 12 to 20 Kg., were used. Under Nembutal anesthesia and using a midline incision, a denervated fundic pouch, as well as a

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denervated antral fistula, was fashioned from the stomach (Fig. 1). Gastrointestinal continuity was re-established by means of a gastrojejunostomy. Following recovery from operation, a meat stimulus was used to determine whether the pouch was capable of secreting acid gastric juice. If this test was positive, the dogs were then subjected to a series of antral perfusions, using various substances known to be capable of stimulating the antrum to release gastrin.

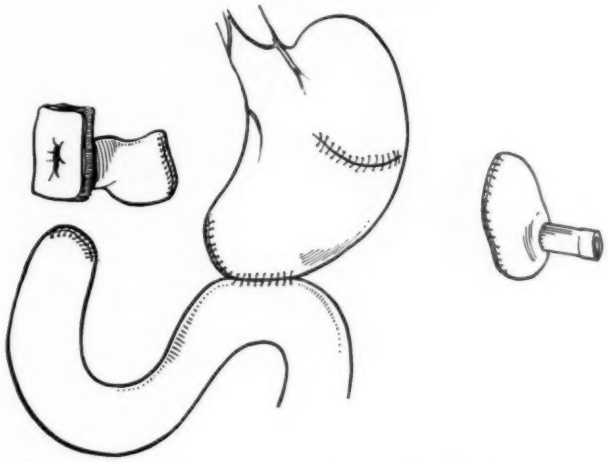

Fig. 1.—Operative preparation with an exteriorized antral fistula *(left)* and a denervated fundic pouch *(right)*. Gastrointestinal continuity re-established by gastrojejunostomy.

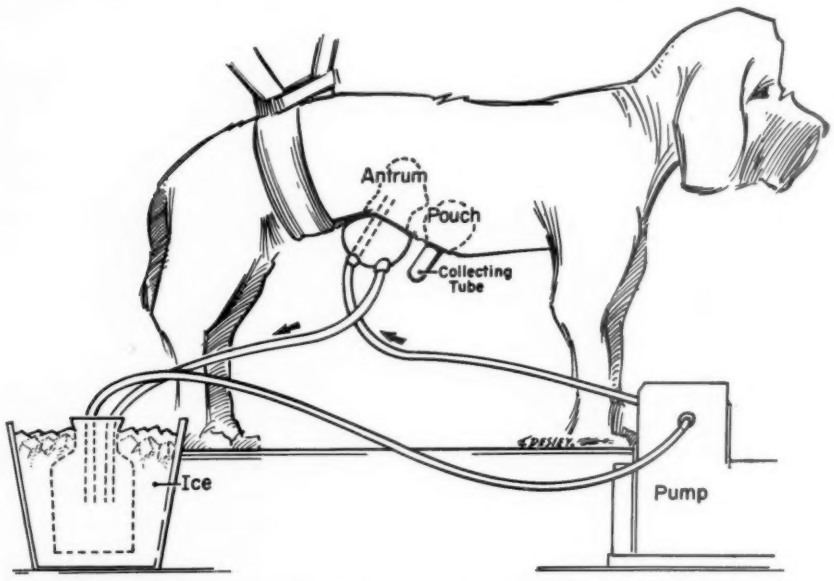

Fig. 2.—Method of constant perfusion of the antral fistula with cold solution using a Sigmamotor pump.

The perfusions were carried out utilizing a Sigmamotor pump and a reservoir, the temperature of which could be maintained at normothermic (38.5° C.) or hypothermic (8° to 10° C.) levels (Fig. 2). In addition to chemical stimulation, the antrum also was stimulated by balloon distention at similar temperatures. The chemicals chosen for study were acetylcholine, 50 mg. per

liter, 5 per cent alcohol, 5 per cent glucose with potassium chloride and ammonium chloride added and buffered to a pH of 7.0 with sodium bicarbonate, and 10 per cent peptone.

The effect of temperature on the acid inhibition of the antrum also was studied. The acid used was 0.1 N HCl.

When the dogs were first placed in the stands, several fasting samples of gastric juice were obtained from the Heidenhain pouch and the pH was determined. Following commencement of the antral perfusion the pH of the juice obtained from the pouch was determined every 15 minutes. When an effect had been noted over a 2½- to 3-hour period, the temperature of the perfusing fluid was altered, and subsequent 15-minute pouch secretions were collected over an additional period of 2½ to 3 hours. All specimens were saved for determination of free acid. At no time was the animal exposed to any possible stimulation by the sight or smell of food.

RESULTS

Tables I and II summarize the findings of this study. A positive response indicates a decrease in the pH of the pouch juice concomitant with the production of free acid, while a negative response means failure of the pouch to secret acid. All dogs responded to perfusion with acetylcholine, 5 per cent alcohol, and 10 per cent petone at normothermic (38.5° C.) temperatures. The

TABLE I. NORMOTHERMIC (38.5° C.) ANTRAL STIMULATION

STIMULANT	NUMBER OF DOGS	NUMBER OF POSITIVE RESPONSES	MEAN TOTAL OUTPUT HCl FOR 3 HOURS (mEq./L.)	NUMBER OF NEGATIVE RESPONSES (NO SECRETION OF ACID)
Acetylcholine	6	6	0.27	0
5 per cent alcohol	5	5	0.14	0
5 per cent glucose + KCl and NH_4Cl (pH 7.0)	4	3	0.04	1
10 per cent peptone	7	7	0.98	0
Balloon	3	3	0.06	0
	25	24		1

TABLE II. COLD (8° TO 10° C.) ANTRAL STIMULATION

STIMULANT	NUMBER OF DOGS	NUMBER OF POSITIVE RESPONSES	MEAN TOTAL OUTPUT HCl FOR 3 HOURS (mEq./L.)	NUMBER OF NEGATIVE RESPONSES (NO SECRETION OF ACID)
Acetylcholine	5	2	0.30	3
5 per cent alcohol	5	1	0.07	4
5 per cent glucose + KCl and NH_4Cl (pH 7.0)	5	0	0	5
10 per cent peptone	6	2	0.10	4
Balloon	3	0	0	3
	24	5		19

response to the latter stimulant was most prompt and vigorous. Only one dog failed to respond to normothermic glucose stimulation. Of 3 dogs submitted to balloon distention of the antrum, at 38.5° C., all responded positively.

When the temperature of the perfusing fluid was maintained at a 8° to 10° C. level, the response to these stimulants was altered considerably. In no instance did the pouches respond to the perfusion of cold *glucose* solution. For the most part the *other* stimulants, when perfused at 8° to 10° C., failed to induce a response from the Heidenhain pouch. One dog consistently showed a

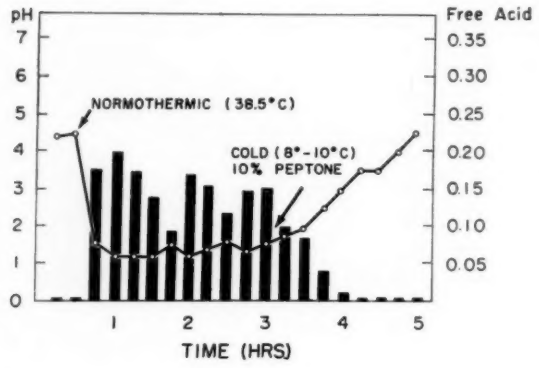

Fig. 3.

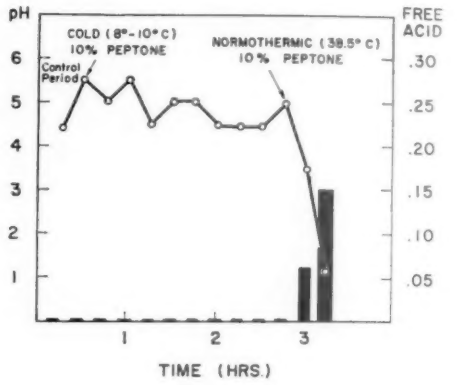

Fig. 4.

Fig. 3.—Typical responses of the normothermic (38.5° C.) fundic pouch to antral perfusion with normothermic 10 per cent peptone followed by cold (8° to 10° C.) 10 per cent peptone.

Fig. 4.—Typical response of the normothermic (38.5° C.) fundic pouch to antral perfusion with cold (8° to 10° C.) 10 per cent peptone followed by normothermic 10 per cent peptone.

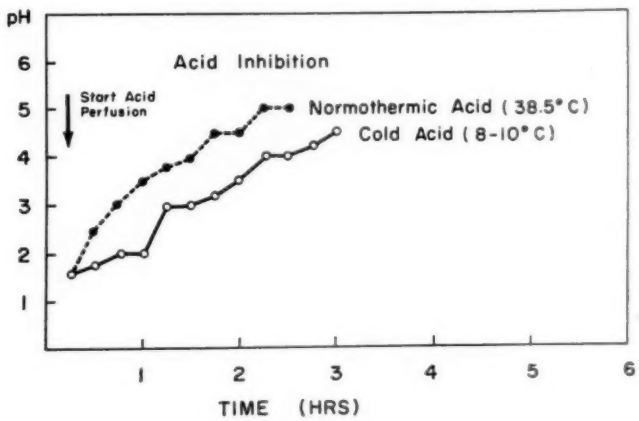

Fig. 5.—Comparison of the response of a secreting fundic pouch to perfusion of the isolated antrum with normothermic and cold acid.

response from the Heidenhain pouch when the perfusate was acetylcholine, alcohol, or peptone, regardless of the temperature. Another dog responded to the perfusion of cold peptone and acetylcholine but not to the perfusion of cold alcohol. The preponderance of negative responses of the pouches to the perfusion of cold solutions, however, is quite significant.

The same 3 dogs stimulated with balloon distention at 8° to 10° C. failed to show acid secretion from the Heidenhain pouch.

Perfusion of the antrum with acid at 38.5° C. after the pouch was responding to any of the stimulatory fluids used demonstrated the typical antral inhibitory response. Decrease of the temperature of the perfusing acid from 8° to 10° C. did not change significantly this inhibitory process. In most cases, the inhibition of the production of acid gastric juice was noticeable within a half-hour of the perfusion and was usually complete when the perfusion had been underway for 2½ to 3 hours. Figs. 3 and 4 show typical responses to stimulatory perfusion, and Fig. 5 demonstrates the relatively little difference in the inhibition produced by normothermic (38.5° C.) or cold (8° to 10° C.) acid.

DISCUSSION

Chemical stimulants elicit a good antral response from isolated Heidenhain pouches of dogs, when perfused at a normothermic temperature at 38.5° C. At hypothermic temperatures of 8° to 10° C., in most instances, similar perfusions fail to produce any response from an isolated warm fundic pouch. On the other hand, similar reduction of the temperature of an acid antral perfusate does not alter significantly the inhibitory responses of the pouch.

One might assume therefore that hypothermia negates the secretagogue effect of food or stimulating solutions upon the antral secretory phase of gastric secretion. The exact mechanism of this inhibition is not clear. Whether this effect is owing to local factors, such as decreased blood flow in consequence of hypothermia, or to the release of an inhibitory substance, remains to be evaluated.

CONCLUSIONS

The response observed in isolated warm fundic gastric pouches upon perfusion of the isolated antrum with warm (38° C.) solutions is inhibited when the dog's antrum is perfused with the same solutions when cold (8° to 10° C.). However, when the antrum is perfused with 0.1 N HCl, the inhibiting effect on acid secretion as observed in warm isolated fundic pouches, is noted whether the antral perfusate is warm or cold.

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INFLUENCE OF GENERAL HYPOTHERMIA AND LOCAL GASTRIC COOLING ON PORTAL BLOOD FLOW

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FACTORS which may alter portal venous flow are important in a variety of surgical conditions and especially in regard to the problem of portal hypertension and bleeding esophageal varices. This investigation was undertaken to study the normal portal blood volume flow and oxygen saturation in the dog and to determine the effect of general body hypothermia and of local gastric cooling.

MATERIALS AND METHODS

Adult mongrel dogs were used. They ranged in weight from 14 to 20 Kg. Anesthesia was accomplished by the administration of intravenous thiopental sodium and respirations were maintained with rhythmic mechanical insufflation of oxygen through an endotracheal tube. Arterial blood pressure was recorded on a mercury manometer from a catheter in the femoral artery and body temperature by a thermocouple inserted in the esophagus or rectum.

Aseptic technique and the electrocautery were used. The portal vein was exposed through a right thoracoabdominal incision in the tenth intercostal space. The few branches entering the portal vein proximal to the splenic vein were ligated and divided. The dog was heparinized by the intravenous injection of sodium heparinate, 1 mg. per kilogram. The portal vein was cross-clamped and divided and thin-walled (5/16 inch) polythene catheters were ligated in place in both the proximal and distal ends of the vein. The blood was allowed to flow freely by gravity drainage from the distal end of the portal vein into a graduated burette and was returned to the proximal end of the portal vein by a Sigmamotor pump adjusted to return the blood at the same rate at which it drained into the burette (Fig. 1). The level of blood in the burette was kept 10 to 15 cm. below the level of the portal vein in order to provide free drainage without collapsing the vein. The burette and tubing were filled with fresh heparinized blood from a donor dog prior to each experiment and the entire system was kept in warm water to keep the dog's body temperature from falling during the procedure. The duration of cross-clamping of the portal vein varied from 3 to 5 minutes.

Portal blood volume flows were recorded by stopping the pump and recording the time required for 50 c.c. of blood to accumulate in the burette. The

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blood flow, arterial blood pressure, and body temperature were measured every 3 minutes during the experiment. Blood samples were taken from the distal catheter every hour in most experiments and the portal venous blood and oxygen saturation were determined by the Roughton-Scholander method. Three groups of dogs were studied.

Group 1. Normothermia.—In 20 normothermic animals the portal vein was cannulated and the blood flow allowed to stabilize for 15 minutes. Normal portal blood flow and oxygen saturation, arterial blood pressure, and esophageal temperature were then determined. In 10 dogs these determinations were made intermittently every 3 minutes over a 2-hour period.

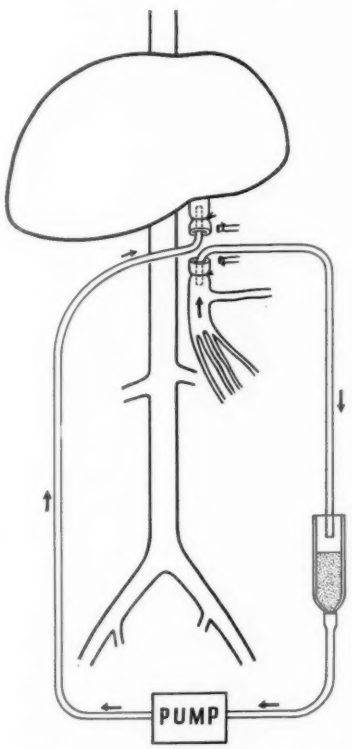

Fig. 1.—Schematic drawing illustrating methods of measuring directly the portal venous volume flow.

Group 2. General Body Hypothermia.—Ten dogs were placed in an ice bath prior to the experimental procedure until their body temperature fell to 33° C. The same study was then carried out as in group 1. Portal blood flows were measured over a 2-hour period during which time the dog's temperature drifted down to a level between 25° and 26° C.

Group 3. Gastric Hypothermia.—In 5 normothermic dogs a rubber balloon attached to a double lumen plastic tube was inserted into the stomach through a small gastrotomy incision. The gastric temperature and the body temperature were followed. The stomach temperature was maintained in the range of 20° C. by filling the balloon with 500 c.c. of ice water which was kept cold by constant circulation through the balloon and through a pail of ice. A Sigmamotor pump was used. The body temperature was maintained as near normal as possible.

This proved to be in the neighborhood of from 34° to 35° C. Portal blood flow, oxygen saturation, gastric and rectal temperatures, and arterial blood pressure were recorded over a period of 2 hours.

RESULTS

In normothermic animals after a period of stabilization the blood pressure averaged 121 mm. Hg. (Table I). In most instances it ranged from 108 to 148 mm. though one animal had a blood pressure of 94. The portal blood flow showed a fairly wide variation, from 22.1 to 45.9 c.c. per kilogram per minute. The mean blood flow was 30.1 c.c. per kilogram per minute. The portal venous oxygen saturation in 12 animals varied from 84.9 to 94.4 per cent and averaged 89.3 per cent.

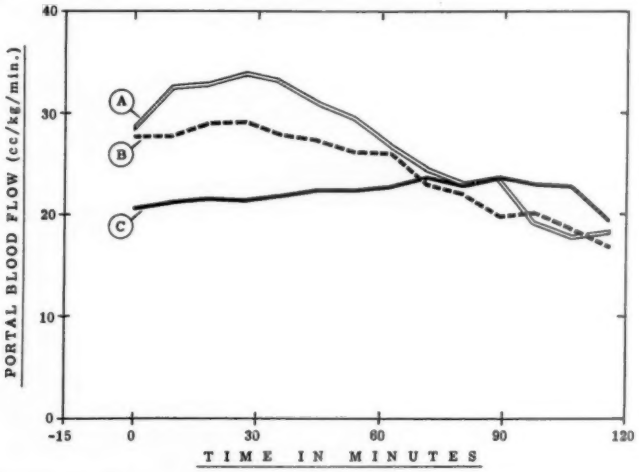

Fig. 2.—Chart showing mean values for portal flow in near-normothermic dogs with local gastric cooling (*A*), in normothermic dogs (*B*), and in moderately hypothermic dogs (*C*).

TABLE I. PORTAL BLOOD FLOW AND OXYGEN SATURATION IN NORMOTHERMIC DOGS AFTER A 15-MINUTE PERIOD OF STABILIZATION

NUMBER OF DOG	ESOPHAGEAL TEMPERATURE (DEGREES C.)	MEAN ARTERIAL BLOOD PRESSURE (MM. HG)	PORTAL BLOOD FLOW (C.C./KG./MIN.)	PORTAL O_2 SATURATION (PER CENT)
1	37.6	130	27.5	94.4
2	36.6	124	32.8	87.0
3	36.8	130	29.7	94.0
4	35.0	94	25.7	91.1
5	37.5	124	43.1	98.9
6	38.5	108	23.1	84.0
7	35.0	108	22.1	82.1
8	35.0	128	31.3	91.5
9	34.0	124	23.6	—
10	36.2	114	22.5	84.9
11	36.9	134	34.2	89.4
12	37.4	132	34.1	86.0
13	38.5	138	23.6	88.1
14	36.3	102	27.2	—
15	36.6	120	33.1	—
16	36.6	100	36.3	—
17	36.6	110	45.9	—
18	38.4	136	28.8	—
19	37.4	148	36.5	—
20	37.2	122	20.2	—
Mean	36.7	121	30.1	89.3

Portal venous flows remained relatively stable during the first hour and then tended gradually to fall (Fig. 2 and Table II). During the third half-hour period the average portal flow was 79 per cent and during the fourth half-hour period 65 per cent of the average values during the first half-hour of study. No significant reduction in oxygen saturation of portal venous blood was observed at the end of the first or second hour.

At the end of the period of stabilization the hypothermic animals had an average body temperature of 28.7°. C. (Table III). The blood pressure was generally in the range between 100 and 124 mm.Hg. In one animal the blood

TABLE II. COMPARATIVE DATA CONCERNING PORTAL BLOOD FLOW AND OXYGEN SATURATION IN NORMOTHERMIC DOGS, MODERATELY HYPOTHERMIC DOGS, AND IN DOGS SUBJECTED TO LOCAL GASTRIC COOLING

NUMBER OF DOG	OXYGEN SATURATION PORTAL BLOOD (PER CENT)			PORTAL VENOUS FLOW (C.C./KG./MIN.)						
							AVERAGE VALUES DURING HALF-HOUR PERIODS			
	INITIAL VALUE	AT END OF 1 HR.	AT END OF 2 HR.	INITIAL VALUE	AT END OF 1 HR.	AT END OF 2 HR.	1ST	2ND	3RD	4TH
Normothermia										
1	94.4	96.0	97.3	27.5	26.6	27.1	27.3	26.8	25.1	27.1
2	87.0	91.0	—	32.8	28.9	23.5	34.7	29.5	26.9	24.3
3	94.0	97.4	94.5	29.7	26.5	17.4	30.5	26.6	26.6	20.7
4	91.1	71.2	96.4	25.7	22.8	13.0	26.7	27.0	19.0	15.3
5	98.9	97.6	77.5	43.1	36.6	16.8	45.4	40.9	29.5	20.5
6	84.0	81.2	71.0	23.1	20.2	11.5	23.0	22.3	17.3	13.7
7	82.1	87.2	80.0	22.1	24.8	18.1	21.4	22.4	22.5	18.2
8	91.5	100.9	100.9	31.3	28.9	20.5	31.0	29.8	27.3	21.9
9	—	—	—	23.6	15.0	9.1	23.7	16.5	12.0	10.2
10	84.9	86.1	81.8	22.5	23.2	12.3	23.2	24.9	20.2	14.4
Mean	89.8	89.8	87.4	28.1	25.4	16.9	28.7	26.7	22.6	18.6
Per cent of original	—	100%	97%	—	90%	60%	—	93%	79%	65%
General hypothermia										
21	89.0	101.0	97.0	16.2	14.7	11.4	16.3	16.9	14.3	12.5
22	84.8	101.2	88.1	25.3	29.1	21.6	28.6	28.9	26.7	—
23	98.0	98.0	96.0	22.3	21.3	19.3	22.7	21.6	19.3	19.1
24	101.0	96.1	91.0	31.6	29.8	24.3	31.4	29.9	27.7	27.1
25	90.9	92.4	91.7	21.3	24.0	24.8	18.1	22.1	24.3	24.8
26	83.5	—	—	17.0	13.4	—	18.1	16.0	—	—
27	101.5	98.2	—	22.8	22.9	—	22.8	23.1	—	—
28	73.5	—	—	12.8	21.7	17.7	13.9	19.2	27.5	27.0
29	71.9	78.3	78.9	19.9	17.7	16.4	17.5	15.2	19.3	15.0
30	93.4	93.4	90.4	26.7	29.1	25.5	28.4	29.9	29.3	27.2
Mean	88.9	94.8	90.4	21.6	22.4	19.9	21.8	22.3	23.1	21.8
Per cent of original	—	106%	102%	—	104%	93%	—	102%	107%	100%
Gastric hypothermia										
31	82.8	77.3	80.6	25.8	31.1	27.9	27.0	31.0	30.1	28.6
32	88.5	98.8	80.3	41.1	35.5	14.8	42.3	41.1	27.1	17.7
33	95.3	95.7	98.1	22.7	17.7	13.0	24.3	22.4	16.4	14.4
34	90.5	91.8	72.1	35.0	37.6	15.2	40.1	39.8	28.3	19.0
35	87.0	85.4	91.3	27.2	22.1	21.8	26.8	24.0	19.4	18.0
Mean	88.8	89.8	84.5	30.4	28.8	18.5	32.1	31.7	24.3	19.5
Per cent of original	—	101%	95%	—	95%	61%	—	99%	76%	61%

pressure was 80 and in another 98; the average was 108. Portal blood flows again varied considerably, from 16.2 to 31.6 c.c. per kilogram per minute. The mean value was 21.6. Portal venous oxygen saturations ranged from 71.9 to 101.5 and averaged 88.9 per cent.

TABLE III. PORTAL BLOOD FLOW AND OXYGEN SATURATION IN MODERATELY HYPOTHERMIC DOGS AFTER A 15-MINUTE PERIOD OF STABILIZATION

NUMBER OF DOG	ESOPHAGEAL TEMPERATURE (DEGREES C.)	MEAN ARTERIAL BLOOD PRESSURE (MM. HG)	PORTAL BLOOD FLOW (C.C./KG./MIN.)	PORTAL O_2 SATURATION (PER CENT)
21	28.8	124	16.2	89.0
22	29.0	98	25.3	84.8
23	26.0	80	22.3	98.0
24	27.0	100	31.6	101.0
25	29.5	120	21.3	90.9
26	28.9	100	17.0	85.3
27	29.7	110	22.8	101.5
28	29.3	124	12.8	73.5
29	29.0	102	19.9	71.9
30	29.5	118	26.7	93.4
Mean	28.7	108	21.6	88.9

Portal blood flows were quite stable in this group (Fig. 2 and Table II). The mean portal blood flow was a trifle more at the end of one hour and only slightly less at the end of 2 hours than the initial value. The average determinations of portal blood flow during the second, third, and fourth half-hour periods were, respectively, 102, 107, and 100 per cent of those obtained during the first half-hour of study. No significant change was noted in portal venous oxygen saturation. The mean value was slightly higher than the original at the end of the first hour and almost precisely the same as the original at the end of the second hour of study.

TABLE IV. PORTAL BLOOD FLOW AND OXYGEN SATURATION ON ANIMALS SUBJECTED TO LOCAL GASTRIC COOLING AFTER A 15-MINUTE PERIOD OF STABILIZATION

NUMBER OF DOG	RECTAL TEMPERATURE (DEGREES C.)	GASTRIC TEMPERATURE (DEGREES C.)	MEAN ARTERIAL BLOOD PRESSURE (MM. HG)	PORTAL BLOOD FLOW (C.C/KG./MM.)	PORTAL O_2 SATURATION (PER CENT)
31	34.6	20.0	120	25.8	82.8
32	35.2	22.5	130	41.1	88.5
33	36.2	19.0	130	22.7	95.3
34	33.8	20.5	120	35.0	90.5
35	34.8	22.0	138	27.2	87.0
Mean	34.8	20.8	128	30.4	88.8

At the end of the period of stabilization the mean body temperature in the animals subjected to local gastric cooling was 34.8° C. (Table IV). The gastric temperature at this time averaged 20.8° C. The mean arterial pressure was 128 mm.Hg and the mean portal oxygen saturation 88.8 per cent. Again a fairly wide variation in portal venous flow was observed. The portal flows varied from 22.7 to 41.1 c.c. per kilogram per minute; the average was 30.4 c.c. per kilogram per minute.

As was true in the control normothermic group, the values for portal venous flow tended to be maintained fairly constantly during the first hour and gradually declined during the second hour of study (Fig. 2 and Table II). Determinations made during the third half-hour period averaged 76 per cent of those during the first half-hour period and during the fourth half-hour period they averaged 61 per cent.

In Table V the mean data are summarized with regard to observations made after the initial period of stabilization. Utilizing information concerning cardiac output obtained in this laboratory from another study,[4] it is evident that, although the animals under general body hypothermia had a mean measured portal blood flow nearly 30 per cent less than that in the normothermic group, the percentage of total cardiac output flowing through the portal venous system was actually greater by approximately 50 per cent. In the normothermic group the portal venous flow was approximately 23 per cent of the total cardiac output and in the hypothermic group approximately 36.5 per cent. The portal venous flow in cubic centimeter per kilogram per minute was almost precisely the same in the normothermic animal and in the near-normothermic animal subjected to local gastric cooling. The portal venous oxygen saturation in all three groups was almost precisely the same.

TABLE V. DATA CONCERNING PORTAL BLOOD FLOW AND OXYGEN SATURATION IN NORMOTHERMIC DOGS, MODERATELY HYPOTHERMIC DOGS, AND IN DOGS SUBJECTED TO LOCAL GASTRIC COOLING

STATE OF ANIMAL	BODY TEMPERATURE (DEGREES C.)	PORTAL BLOOD FLOW		OXYGEN SATURATION (PER CENT)
		C.C./KG./MIN.	PER CENT OF CARDIAC OUTPUT	
Normal	36.7	30.1	23.2	89.3
General body hypothermia	28.7	21.6	36.5	88.9
Local gastric cooling	34.8	30.4	27.0	88.8

DISCUSSION

The method of measuring directly portal venous flow described seems to be an accurate one. Values remained relatively constant during the first hour of study. Considerable variation, however, was observed from one animal to another. The mean value is similar to that obtained by Fisher and his associates[3] who measured hepatic venous blood flow indirectly with the Bromsulphalein technique. They found the average estimated hepatic blood flow in anesthetized dogs to be 49 plus or minus 7.4 c.c. per kilogram per minute. If, as has been suggested, there is a possible 11 per cent error in this figure due to extrahepatic absorption of the dye and if, as has also been suggested, 70 per cent of the estimated hepatic blood flow is contributed by portal venous flow, one would calculate from these data that the estimated portal venous flow was 30.8 c.c. per kilogram per minute. Our mean value was 30.1 c.c. per kilogram per minute. These values are somewhat higher than those reported by other investigators. In 1911 Burton-Opitz[2] reported an average flow of 18.8 c.c. per kilogram per minute using a stromuhr, and in 1936 Blalock and Mason[1] recorded an average flow of 21.6 c.c. per kilogram per minute in unanesthetized dogs by direct measurement of hepatic flow with the hepatic artery occluded. More recently, in 1958,

Stewart and his colleagues[5] found an average flow of 24.6 c.c. per kilogram per minute in anesthetized dogs using a square-wave electromagnetic flowmeter.

Animals subjected to general body hypothermia maintained a much more constant portal venous blood flow during the 2-hour period of observation. At an average body temperature of slightly less than 29° C. the mean portal blood flow was approximately 70 per cent of that observed in the normothermic group. The portal blood flow, however, in the hypothermic animals represented approximately 36 per cent of the total cardiac output and only 23 per cent in the normothermic animals.

Local cooling of the stomach did not seem to affect the portal blood flow. The mean value, indeed, in animals subjected to local gastric cooling was almost precisely the same as that observed in the control animals. Wangensteen and his associates[6] have observed a sharp decrease in gastric blood flow per se during local gastric cooling. If both observations are correct, one must assume that there is some compensatory blood flow into other portions of the splanchnic bed during local gastric cooling. The saturation of the portal venous blood was almost precisely the same in our normothermic animals, those maintained at moderate hypothermic levels, and those subjected to local cooling of the stomach. This observation gives us no lead as to whether gastric arteriovenous shunts may open or close during local cooling. If any change does occur in gastric arteriovenous shunts, one would have to assume that compensatory changes occur in other portions of the splanchnic bed. Since many patients with bleeding esophageal varicosities have markedly impaired hepatic function, it is comforting to know that the total portal venous flow in the normal dog is not reduced during local gastric cooling.

SUMMARY

1. An apparently accurate and relatively simple method for measuring directly portal blood flow has been described. In normal, well-ventilated, lightly anesthetized dogs, determinations of portal blood flow remain relatively stable over a one-hour period. Fairly wide variations, however, are observed in different animals.

2. In normothermic animals the mean portal blood flow is 30.1 c.c. per kilogram per minute. This represents approximately 23 per cent of the total cardiac output. Under moderate general hypothermia the portal blood flow is 21.6 c.c. per kilogram per minute, or approximately 70 per cent of the mean value observed in normothermic animals. This represents, however, 36.5 per cent of the hypothermic dog's normal cardiac output. Portal blood flow determinations are remarkably stable in the hypothermic animal over a period of 2 hours. With the body temperature maintained at near-normal levels, and the stomach cooled locally, the mean portal blood flow is practically identical to that observed in the control group (30.4 c.c. per kilogram per minute).

3. Oxygen saturation of portal venous blood is almost precisely the same in the normothermic animals, in the hypothermic animals, and in those subjected to local gastric cooling.

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STUDIES ON THE EFFECT OF INTRAGASTRIC COOLING ON ACUTE EXPERIMENTAL PANCREATITIS

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THE exact etiology and pathogenesis of acute hemorrhagic pancreatitis in man has not been clearly defined and is still the subject of many theories, the most prominent of which seem to be based on the common channel theory of Opie.[2] Similarly the treatment of this disease is not completely satisfactory and has been largely aimed at controlling the effects of the internal inflammatory reaction of the pancreas with the use of fluids, electrolytes, and colloid replacement.

Since the activity of the exogenous pancreatic enzymes (especially trypsin) seems to be intimately associated with the development and perpetuation of acute pancreatitis, any depression of these enzymes could be expected to affect favorably the course of the disease. That enzymatic activity is depressed by lowering the environmental temperature is a well-accepted fact. It seemed logical, therefore, to study the effect of regional cooling of the pancreas on acute pancreatitis. While to our knowledge, experimental work on this subject has not been published, Wangensteen and his associates[4] have indicated that they are presently working along similar lines.

In the present study, dogs with bile-induced pancreatitis were subjected to intragastric cooling and the short-term effects were compared to normothermic controls.

METHODS

Production of Pancreatitis.—Healthy mongrel dogs weighing 15 to 34 pounds were anesthetized intravenously with Nembutal. An upper midline abdominal incision was used. The major pancreatic duct was cannulated with a No. 50 polyethylene tube at a point immediately proximal to its entrance into the duodenum. The lesser pancreatic duct was ligated to prevent drainage into the duodenum. Ten cubic centimeters of bile aspirated from the gall bladder was injected into the main pancreatic duct at a constant pressure of 400 to 450 mm. Hg.

Production of Intragastric Cooling.—Immediately following the induction of acute pancreatitis, intragastric cooling was instituted. A thin-walled balloon attached to a double lumen polyvinyl tube was inserted into the dog's stomach via the mouth. The internal diameter of the intake tubing was 4 mm. and the outflow was 10 mm. Water cooled by ice or ice-salt slush was circulated through

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the balloon by a small electric centrifugal pump. Simultaneous temperatures of the balloon, gastric wall, pancreas, and rectum were monitored periodically. The temperature of the pancreas was obtained by a small thermistor needle inserted into the body of the pancreas. The downward drift of the systemic (rectal) temperature was effectively stopped by placing a Thermorite warming blanket beneath the back of the shaved animal.

Determinations.—The effect of intragastric cooling on experimentally induced pancreatitis was assessed by: (a) hourly determination of amylase and lipase in pancreatic venous blood, peripheral venous blood, and intra-abdominal fluid; (b) hourly measurement of intra-abdominal fluid volume; and (c) gross and microscopic appearance of the pancreas at the time of sacrifice 4 hours following induction of pancreatitis.

For amylase determination, the method of Somogyi[3] was modified to give an accurate end point. The reaction at 37° C. between 1.0 ml. of a 1 to 10 dilution of dog serum and 4.0 ml. starch solution was followed by withdrawing 0.5 ml. samples at timed intervals into 5.0 ml. aliquots of dilute iodide solution (a 1 to 10 dilution of Somogyi's solution, with 1 part of 2.5 M potassium fluoride added per 50 parts dilute solution). The resulting blue starch-iodide color was read against a reagent blank at 700 mμ in a Coleman Junior spectrophotometer. The end point of the reaction corresponding to that of Somogyi's was taken as the time required for the optical density to drop to 10 per cent of its initial value (determined with 0.4 ml. of starch solution and 0.1 ml. of distilled water added to 5.0 ml. dilute iodide solution) and was read from a graph of optical density plotted against time of reaction. The lipase determination followed the method of Henry,[1] in which an olive oil emulsion is broken down to fatty acids which are titrated with standard alkali.

RESULTS

Acute pancreatitis was induced in a group of 9 dogs under normothermic conditions. Yellow discoloration and interlobular edema of the pancreas occurred within 5 minutes of the bile injection. This was followed by the appearance of bloody peritoneal fluid. In the second hour small flecks of fat necrosis appeared in the duodenal mesentery; small centrilobular ecchymoses were seen in the pancreas and these lesions generally increased in size. These animals served as controls.

In a second group of 8 dogs, intragastric cooling was instituted shortly after pancreatitis was induced. Temperatures of the rectum, pancreas, gastric wall, and intragastric balloon are shown in Fig. 1. It is to be noted that the average pancreatic temperature during a 4-hour period of intragastric cooling was 7.4° C. below rectal temperature. In addition, a downward drift of the systemic (rectal) temperature averaged 4.2° C. below normal (37° C.). In each experiment it was necessary to use the warming blanket (at temperatures ranging from 51° to 60° C.) to prevent further systemic cooling. At times when the temperature of the blanket reached high levels, the systemic temperature increased. This was usually associated with a slight increase in the pancreatic temperature.

Comparison of the effects of experimental acute pancreatitis in the normothermic and hypothermic dogs revealed impressive differences. Intragastric cooling resulted in a decrease in the volume of intraperitoneal fluid to an average maximal level of less than one-half of that seen in normothermic dogs. In addition, cooling reduced the lipase content of the peritoneal fluid to 44 per cent of that found in the normothermic animals (Fig. 2).

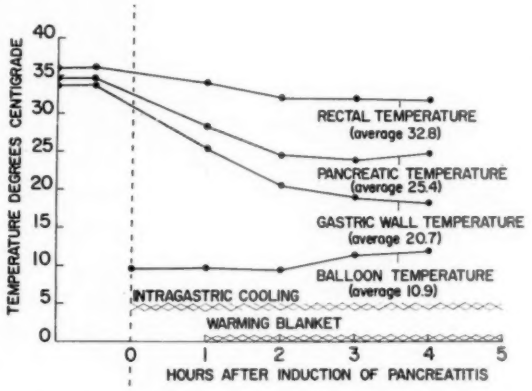

Fig. 1.—The average hourly temperatures of the rectum, pancreas, gastric wall, and balloon in a series of 8 dogs subjected to intragastric cooling following the induction of pancreatitis.

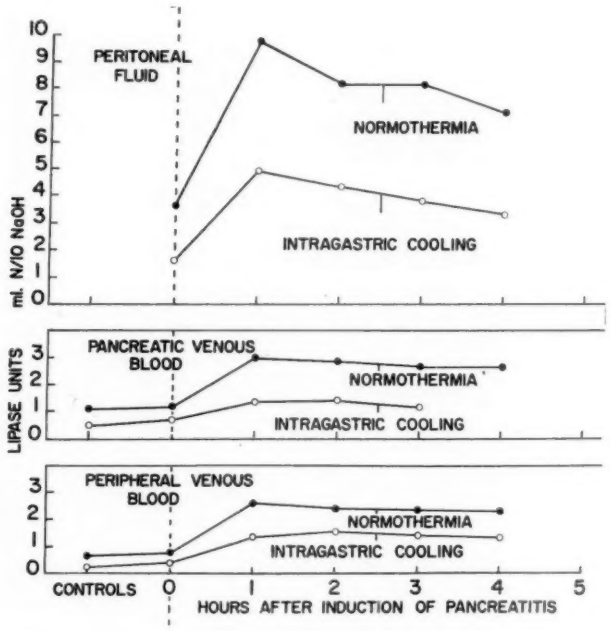

Fig. 2.—Comparison of the average hourly lipase values in the peritoneal fluid, pancreatic venous blood, and peripheral venous blood of the normothermic and cooled animals.

Experimental pancreatitis caused a three- to fourfold increase in lipase and amylase levels of femoral and pancreatic venous blood; hypothermia approximately halved this increase both in lipase and in amylase values (Figs. 2 and 3). The range of these values is shown in Table I.

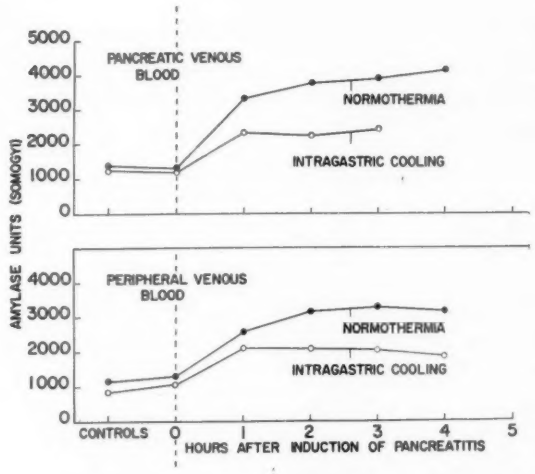

Fig. 3.—Comparison of the average hourly amylase levels in the pancreatic and peripheral venous blood of the normothermic and cooled animals.

TABLE I. RANGE OF LIPASE AND AMYLASE VALUES BEFORE AND AFTER INDUCTION OF EXPERIMENTAL PANCREATITIS

		NORMOTHERMIA		INTRAGASTRIC COOLING		NORMOTHERMIA		INTRAGASTRIC COOLING	
		LIPASE (ML. $\frac{N}{10}$ NaOH)	NUMBER OF DOGS	LIPASE (ML. $\frac{N}{10}$ NaOH)	NUMBER OF DOGS	AMYLASE (SOMOGYI UNITS)	NUMBER OF DOGS	AMYLASE (SOMOGYI UNITS)	NUMBER OF DOGS
Peripheral blood									
Before pancreatitis									
Control, approx.	1 hour	0.1- 1.4	9	0.1-0.6	8	950-1,390	4	740-1,190	5
Control	0 hour	0.2- 1.4	6	0.1-0.7	6	920-1,720	4	820-1,280	5
After pancreatitis									
	1 hour	1.1- 5.0	9	0.9-2.2	8	1,880-3,900	4	1,480-3,100	5
	2 hour	1.4- 4.3	9	0.8-3.0	8	2,460-4,210	4	1,370-2,690	5
	3 hour	1.4- 4.2	9	0.7-2.2	8	2,210-4,110	4	1,000-2,710	5
	4 hour	1.4- 4.0	9	0.5-3.0	8	1,780-4,270	4	900-2,990	5
Pancreatic vein blood									
Before pancreatitis									
Control, approx.	1 hour	0.4- 1.6	9	0.3-0.8	4	1,020-1,840	4	1,200-1,570	2
Control	0 hour	0.5- 1.7	6	0.2-1.4	4	1,020-1,680	4	1,050-1,640	3
After pancreatitis									
	1 hour	1.1- 5.5	8	0.6-2.2	5	3,080-3,900	3	1,640-3,110	3
	2 hour	1.0- 5.6	8	0.8-2.0	5	3,480-4,320	3	1,620-2,910	3
	3 hour	1.1- 5.2	8	0.6-1.9	4	3,560-4,210	2	1,180-3,640	2
	4 hour	0.6- 5.6	8			3,560-4,570	3		
Peritoneal fluid									
Before pancreatitis									
Control, approx.	0 hour	1.1- 6.0	2	0.7-1.9	4				
After pancreatitis									
	1 hour	6.8-14.1	9	1.4-9.0	8				
	2 hour	4.3-12.5	9	1.2-8.2	7				
	3 hour	4.0-11.8	9	1.0-8.0	8				
	4 hour	3.1-11.4	9	1.6-6.8	7				

The amount of visible intraperitoneal fat necrosis was appreciably less in the hypothermic dogs. Microscopic sections of the pancreas of all animals revealed focal necrosis of acute hemorrhagic pancreatitis. The only difference observed between the hypothermic and normothermic groups was a decreased polymorphonuclear infiltration into the acinar tissue of the cooled group.

DISCUSSION

In attempting to determine the value of intragastric cooling in acute pancreatitis, we encountered several basic questions. First, is it possible to cool the pancreas regionally without incurring a similar amount of general hypothermia? Second, does the degree of pancreatic hypothermia produced result in decreased pancreatic enzyme activity in the blood and peritoneal fluid? Third, what is the effect of intragastric cooling on the morbidity and mortality of acute pancreatitis? Regarding the first two questions, our results are affirmative. Since all the experiments in this study were acute, the third question awaits additional work.

Intragastric cooling resulted in a definite drop in the systemic (rectal) temperature in each instance, but this was effectively controlled with external heat. The animal's systemic temperature hung in balance between the influences of the cooling balloon and warming blanket. During this period we were able to achieve a degree of pancreatic hypothermia ranging from 6.5° to 13.6° C. below the rectal temperature and 11.0° to 20.3° C. below normal (37° C.). Using intragastric cooling in dogs (gastric temperature in the range of 17° to 20° C.), Wangensteen and co-workers[4] observed that the temperature 1 to 2 cm. away from the gastric wall was only 1° to 2° C. lower than the rectal temperature. This observation seemed to discourage any hope of attaining an appreciable degree of regional cooling of the pancreas. However, the greater pancreatic-rectal temperature differential obtained in this study is believed to have resulted from the proximity of the posterior aspect of the stomach to the body of the pancreas with only the thickness of the gastric wall (approximately 3 mm.) separating the balloon from the pancreas. It is of interest to note that a greater portion of the pancreas of the human, in comparison with that of the dog, is in contact with the posterior aspect of the stomach.

In the present study a statistically significant depression of lipase and amylase activity was obtained in the cooled animals.* Presumably trypsin was inhibited in a parallel manner, although tests for this enzyme were not performed in this preliminary study. Since the pathogenesis of acute pancreatitis is poorly understood, the exact effect of this degree of pancreatic enzyme inhibition on the course of the disease is difficult to predict.

An interesting observation in the hypothermic animals was the decreased accumulation of intra-abdominal fluid. This finding may, in part, be due to the diminished blood supply of the cooled region.

*When the results obtained in the mid-portion of the experiment (second hour) were tested by the standard t-test, all three sets of lipase values (for peripheral venous blood, pancreatic venous blood, and peritoneal fluid) and both sets of amylase values (for peripheral venous blood and pancreatic venous blood) showed significant differences at or below the 5 per cent level.

Wangensteen and associates[4] found that the gastric secretion of pepsin and HCl was decreased by approximately 75 per cent during intragastric cooling. This depression of stomach secretion should largely remove the stimulus for the elaboration of secretin. Depression or elimination of this important humeral stimulant of the pancreas may have a salutary effect on acute pancreatitis.

Chronic experiments will be undertaken to observe the effect of intragastric cooling on the morbidity and mortality of experimentally induced pancreatitis.

SUMMARY

The effects of intragastric cooling on acute pancreatitis induced in dogs were compared to a normothermic control group. In the cooled animals the following was observed:

1. Amylase and lipase levels in the peripheral venous blood, pancreatic venous blood, and intra-abdominal fluid were reduced by approximately 50 per cent.

2. The volume of intra-abdominal fluid was reduced by approximately 50 per cent.

3. The average pancreatic temperature was 7.6° C. below the systemic temperature. Although systemic hypothermia occurred, it was controlled with a warming blanket.

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SEGMENTAL GASTRECTOMY WITH INNERVATED ANTRUM FOR DUODENAL ULCER

Results at One to Five Years

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ALTHOUGH it is agreed that the goal of surgery for duodenal ulcer is to reduce the amount of acid reaching sites of actual or potential ulceration, a number of different operations are in common use. Secondary considerations, among which ability of the patient to eat without discomfort after surgery is perhaps foremost, determine the choices of procedure. Where the patient's comfort is concerned, a divergence of opinion as to the results of various types of operation is scarcely to be wondered at, except that it has continued for so many years without much attempt to resolve it by more objective methods. In the present study the double-blind technique has been used to assist in evaluating a type of segmental gastrectomy for duodenal ulcer, by comparing this operation with a standard Billroth II type of resection. The segmental operation, previously reintroduced by Wangensteen,[6] was modified to preserve innervation and avoid pyloroplasty, on the assumption that a normally functioning antrum and pylorus might alleviate postgastrectomy symptoms.

PATIENTS STUDIED

There were 311 male veterans consecutively operated upon for duodenal ulcer in this hospital between Nov. 18, 1953, and Dec. 27, 1957. At first the Billroth II operation was used predominantly, the segmental operation was performed only occasionally and at random so far as medical indications were concerned. In 16 patients a Billroth I operation was performed. This operation was not used after 1954, and these patients are not included in the study. Early enthusiasm for the segmental operation, based on results in the first 23 cases operated upon prior to July 1, 1954, was followed by a period of one year when this operation was used exclusively. The larger number of segmental resections in the study resulted from this circumstance. Realization that this choice was not convincingly justified finally led to re-establishment, on July 1, 1955, of randomization, now in two equal groups by hospital number, between segmental and Billroth II operations. It would have been preferable to randomize from the beginning by the use of cards drawn after operability was determined. Comparison of the characteristics of the two groups studied as listed in Table I does not indicate any significant bias, however, and no reason is known to think that such occurred. The indications for surgery were determined by medical-surgical consultation and are listed in Table I.

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TABLE I. COMPARISON OF PATIENT GROUPS

	SEGMENTAL (185 PATIENTS)	BILLROTH II (110 PATIENTS)
Average age, operation	46 years	49 years
Average duration symptoms	14 years	14 years
Indication for surgery		
Pain alone	23%	18%
Pain, obstruction	6%	8%
Pain, previous perforation	11%	5%
Pain, bleeding	7%	5%
Pain, also gastric ulcer	1%	1%
Obstruction	16%	24%
Bleeding, not emergency	28%	26%
Bleeding, emergency	8%	11%
Perforation	0%	2%

METHODS

The operation conveniently referred to as the Billroth II type was performed in a standard fashion. About 75 per cent of the stomach was resected, including almost the entire lesser curvature, and a short loop retrocolic partial inferior end-to-side gastrojejunostomy was made. Postoperative insulin hypoglycemia tests usually produced no secretory response, suggesting that the pouch was largely denervated, as would be expected with removal of the lesser curvature.

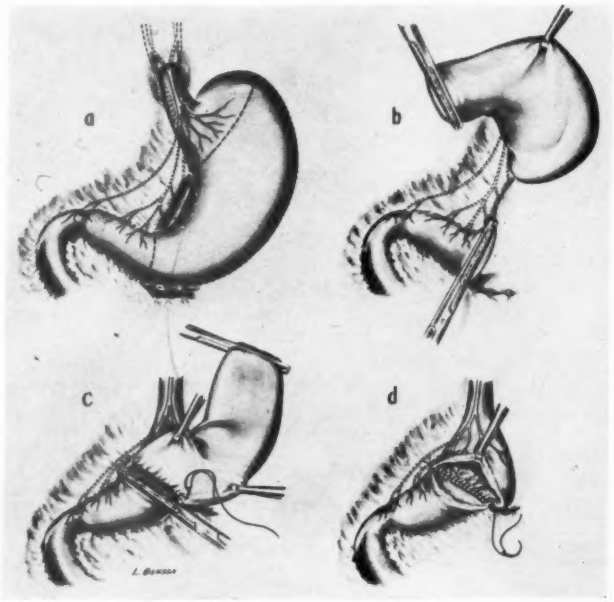

Fig. 1.—Drawing of steps in segmental gastrectomy, showing method of preserving vagal innervation.

The segmental operation was designed to conserve the pylorus and the vagal innervation of both fundic and antral pouches (Fig. 1). The gastrohepatic omentum was divided where it joined the muscle of the lesser curvature, and no clamps were used on the upper pouch. All short gastric vessels were divided and a long length of greater curvature was thus removed, while a much smaller portion of the lesser curvature was excised (Fig. 2). In 28 per cent of patients

undergoing the segmental operation, a duodenal stricture was present, of a size that would not admit a finger. In these patients a 2 to 3 cm. longitudinal duodenotomy was made, rarely extending to the pylorus, and was closed transversely. If the ulcer had bled within a day or 2 prior to surgery, it was exposed and bleeding points were ligated. The mucosa was sutured after slight undermining of the edges. Weights of stomach resected are given in Table II. Measurements of residual pouch size (Fig. 2) were made using the pylorus and the lateral margins of the esophageal hiatus as landmarks. It would be better to find the cardia, but that cannot be done accurately without inspecting the mucosa. In 3 autopsy specimens, the upper pouch weighed from 20 to 30 grams and the lower 15 to 33 grams. The operations were performed by various senior residents and staff members.

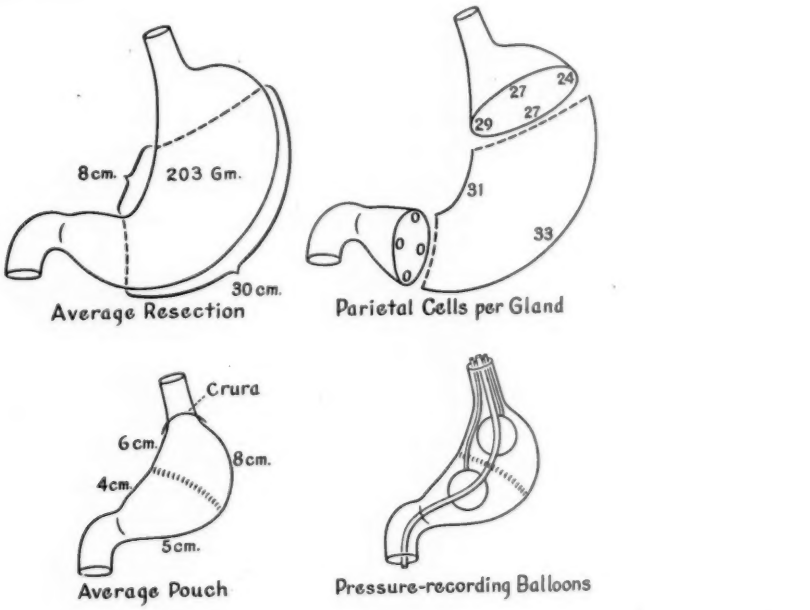

Fig. 2.—Diagrams indicating average sizes of resected segment and residual pouches, using the pylorus and the lateral edges of the esophageal hiatus as landmarks. Average parietal cell counts from 10 specimens are indicated, as is the position of balloons placed at operation for motility studies.

TABLE II. WEIGHT OF STOMACH RESECTED

	SEGMENTAL			BILLROTH II		
	PER CENT	MEAN	RANGE	PER CENT	MEAN	RANGE
Without palpable obstruction	72	192 Gm.	90-375	76	212 Gm.	107-372
With palpable obstruction	28	231 Gm.	116-355	24	263 Gm.	170-402
Whole group		203 Gm.	90-375		224 Gm.	107-402

Evidence of vagal innervation of the pouches after segmental resection was perhaps most convincingly demonstrated anatomically: the nerve fibers to both antrum and fundus were observed to be intact whenever they were carefully sought at the close of the operation.

Functional tests were performed in 15 patients with the aid of balloons fixed to the nasal tube and placed in the pouches at operation (Fig. 2). On the fifth postoperative day the balloons were connected to strain gauges and inflated until respiratory pressure changes gave small deflections (Fig. 3). Occasional larger pressures were observed in addition, from contraction of the pouches. Insulin was injected intravenously in a dose of 0.25 U. per kilogram. Continuous aspiration and periodic analysis of the gastric secretion was made. In 10 of the 15 patients a burst of motor activity was observed in the antral pouch at about 30 minutes after injection. Periods of apparent inhibition of the resting activity were also observed in both pouches. Fundic pouches were responsive in only 6 of these patients, but an additional 2 showed an increased secretion of acid at the time of the antral motor response. There seemed to be a sequential relationship between contractions in the two pouches, without complete coordination (Fig. 3). Blood sugars fell to one half or less of the control value in these patients, but this measurement did not always coincide with the increased motor activity of the pouches. Symptoms of hypoglycemia were also observed. The increased motility after insulin is most reasonably interpreted as evidence of vagal innervation, on the basis of analogy with similar findings observed in dogs,[1] though other relevant studies in human beings have given contradictory results.[4, 5] Negative findings in a single test of this kind have little significance.

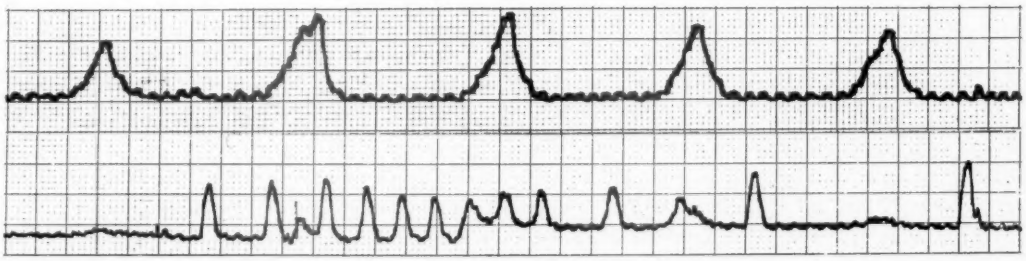

Fig. 3.—Pressure tracing from balloons in fundus *(upper line)* and antrum about 30 minutes after injection of insulin in a patient who had segmental resection 5 days before. Duration of tracing is 5½ minutes, at the height of the reaction. The 1 mm. deflections correspond to respiratory movements. Throughout the period beginning before injection of insulin and continuing for 1 hour afterward there was no other comparable activity, only occasional smaller deflections.

Finally, there were no instances of severe postoperative gastric retention, such as have occurred with segmental resections in which the antrum was denervated without the addition of a pyloroplasty.[6] It seems probable then that effective innervation was normally preserved by the version of segmental resection used in this study.

Biopsies of the gastric mucosa from the 10 locations indicated in Fig. 2 were taken from 10 patients at operation, serially sectioned, and stained with hematoxylin and eosin. The number of nucleated parietal cells sectioned in those glands which could be seen in one plane from the bottom of a pit to the muscularis mucosae were counted. Averages for the 10 patients are given on Fig. 2. The zeros around the antral edge indicate that this line of resection

was consistently below the acid-secreting area. The upper line appears to be above the area of maximal parietal cell concentration, in accordance with the distribution of these cells found by Berger.[2]

Follow-up studies, in addition to close questioning of patients about their symptoms and ability to work, included measurement of body weight and hemoglobin. Barium contrast x-rays were taken at 2 to 3 weeks, 3 months, 6 months, and yearly thereafter to 5 years. There were 6 patients who made no follow-up visits, and 20 more who were observed for less than 1 year before they were lost.

One of us who had no other acquaintance with the patients, and did not know which operation had been done, conducted a single interview with each of 84 patients who had had segmental resection and 51 who had had the Billroth II procedure. All had been followed 1 to 4 years, but otherwise represented consecutive follow-up visits from the total group of patients. All patients were asked the same questions, including whether they were having any of the complaints listed in Table VI. The complaint was noted to be present or absent, regardless of severity, frequency, or whether it was provoked by admitted overeating or drinking. This appeared to be the most objective way to compare the two groups, though it gives an exaggerated idea of the amount of symptomatology. Patients were given repeated advice about dietary problems, and a variety of prescriptions for iron and vitamins; also antispasmodics, mild sedatives or tranquillizers, and so forth, if the symptoms were severe.

RESULTS

The most striking general observation was that the results with these two quite different operations were not easily distinguished. Comparison of mortality, recurrence of ulcer, and postoperative symptoms gives no clear indication of superiority of one procedure over the other (Tables III-VI).

Mortality in the segmental group included 3 operative or postoperative deaths, all in patients operated upon as an emergency for bleeding; the corresponding subgroup accounted for 3 of the 5 deaths in the Billroth II group. The remaining 2 deaths occurred in patients operated upon for obstruction, and were both due to staphylococcal enteritis. The 6 hospital deaths in bleeding patients were attributed to hemorrhagic and surgical shock, aspiration of gastric contents, hepatitis and uremia, hemorrhagic enteritis, coronary thrombosis, and myocardial infarction. None of these seems to have been related to the type of operation performed. (Subsequent to this study, staphylococcal enteritis has occurred after segmental resection.) Postoperative complications were similarly unrelated to the procedure used. No leakage of a duodenal stump (or of a duodenotomy closure) was demonstrated.

Recurrence or persistence of ulcer was suspected whenever typical pain occurred or melena was reported. The x-rays at 2 to 3 weeks in the segmental group practically always showed disappearance of a crater if one had been present preoperatively or at surgery. The suggested presence of a crater was observed later on in 4 per cent of each group, but not all these patients had symptoms (Table IV). In those without symptoms the x-ray finding has persisted unchanged, and is thought to be a deformity due to scar. One patient

TABLE III. HOSPITAL MORTALITY

	SEGMENTAL (185 PATIENTS)	BILLROTH II (110 PATIENTS)
Total mortality	1.6%	4.5%
Mortality after elective surgery	0.0%	1.8%

TABLE IV. SIGNS AND SYMPTOMS SUGGESTING RECURRENT OR STOMAL ULCER AT ANY TIME 3 MONTHS TO 5 YEARS AFTER OPERATION

	SEGMENTAL (177 PATIENTS)	BILLROTH II (104 PATIENTS)
Possible crater, x-ray		
With pain	2%	1%
With melena	0	2
Asymptomatic	2	1
Ulcer type pain	16	8
Melena	2	4
Unexplained anemia	1	2
Gastric ulcer	1	0

TABLE V. AVERAGE CHANGES IN BODY WEIGHT IN PATIENTS FOLLOWED 4 YEARS AFTER OPERATION

TIME AFTER OPERATION	SEGMENTAL (50 PATIENTS)	BILLROTH II (22 PATIENTS)
5 days	147 lb.	151 lb.
3 months	138 lb.	142 lb.
1 year	142 lb.	143 lb.
4 years	149 lb.	148 lb.
Over 10 per cent loss at 4 years	3/50 6%	5/22 23%
Individual changes 5 days → 4 years	179 → 160 lb.	127 → 100 lb.
	189 → 143 lb.	150 → 128 lb.
	195 → 164 lb.	154 → 138 lb.
		163 → 135 lb.
		165 → 138 lb.

TABLE VI. COMPARISON OF POSTOPERATIVE SYMPTOMS

	REGULAR FOLLOW-UP				BLIND FOLLOW-UP	
	3 MONTHS		3-5 YEARS		1-4 YEARS	
	SEGMENTAL (151 PATIENTS)	BILLROTH II (85 PATIENTS)	SEGMENTAL (108 PATIENTS)	BILLROTH II (45 PATIENTS)	SEGMENTAL (84 PATIENTS)	BILLROTH II (51 PATIENTS)
No complaint	21%	27%	35%	40%	40%	24%
Bleeding	0	0	0	2	0	0
Ulcer pain	4	2	5	9	7	4
Substernal pain	16	5	24	11	19	14
Nausea, regurgitation	29	32	25	24	19	20
Cramps	14	11	11	11	5	22
Diarrhea	6	6	10	9	11	20
Faintness	41	38	23	18	21	31
Fullness	28	19	11	7	11	16
Palpitation	9	9	3	13	5	14
Sweating	38	32	26	29	19	45
Tiredness	5	7	4	2	4	2

had ulcer-type pain and a persistent deformity of the duodenum interpreted as an ulcer crater, 5 months after a segmental resection. Exploration, with duodenotomy, was performed at a time when symptoms were present. No sign of an ulcer was found. A small hiatal hernia was repaired. At 16 months there was no further complaint of ulcer pain, but the patient complained of occasional substernal pain and nausea. Exploration of another segmental patient with persistent ulcer symptoms and crater at 4 months revealed that the initial resection failed to include the part of the fundus supplied by the upper three short gastric vessels, and therefore too large a pouch remained. The duodenal ulcer had failed to heal. A satisfactory result was obtained by resecting the ulcer and 84 grams of stomach (including the antrum), with a Billroth I anastomosis. The remaining patients with possible symptomatic recurrence of ulcer have responded to medical management, except for one who has been lost to follow-up.

Postoperative symptoms were evaluated by many different individuals during routine follow-up visits. The data in Table VI summarize all positive findings at 3 months and at the last visit made during 3 to 5 years after operation, as recorded on the charts. The blind follow-up data are also listed for comparison. If there were a consistent bias on the part of the regular examiners, it presumably would be revealed by a difference between the regular and blind follow-up data. (Regular examiners were aware that a blind follow-up was also being made.) Taking into account the wide variability in complaints listed by the same patients at different times in their courses, there seem to be no important differences between results of the two methods of follow-up, except perhaps in regard to substernal pain. This complaint was early associated with the segmental operation and was often discussed by the hospital staff. Possibly it was sought more diligently among the segmental patients during regular follow-up visits, since its apparent predominance in this group was not well confirmed by blind follow-up. Esophagoscopy was rarely employed in these patients, since the complaint usually responded to avoidance of recumbency immediately after eating, taking of smaller more frequent meals, and occasional use of antacid. In two patients with esophagitis verified by endoscopy who had had segmental resection, exploration revealed small hiatal hernias, the repair of which was followed by improvement in symptoms.

Palpitation and perhaps sweating and abdominal cramps were more commonly observed after the Billroth II operation, suggesting that they may be specifically related to rapid passage of food into the jejunum.

Changes in average body weight (Table V) are similar in the two groups, both showing a tendency to rapid loss during the first few months with gradual recovery to about the original level in 4 years. The individual changes of those losing over 10 per cent of their initial weight, listed in Table V, suggest that there was more serious difficulty after the Billroth II operation.

Postoperative anemia, hemoglobin below 13 Gm. per cent, was observed at some time in 10 per cent of segmental patients and 15 per cent of Billroth II patients. In most of these hemoglobin promptly rose above 13 Gm. with administration of iron. Excluding those with other serious disease, there were 5

Billroth II patients and 1 segmental patient with hemoglobin below 12 Gm. Three of the former group had other evidence of recurrent ulcer, and are included under other headings in Table IV; the remaining 3 are listed under anemia in this table, on the assumption that recurrent ulcer may have been present.

The ability of patients to work after operation depended on many factors other than postgastrectomy symptoms. Some patients worked sporadically. The simplest objective evaluation of the data seemed to be obtained by eliminating those over age 60, who often were retired, and those with other serious diseases, and tabulating the numbers of the remaining patients who did no gainful work after surgery. On this basis there were 2 per cent in the segmental group and 6 per cent in the Billroth II group who failed to work at all after surgery. The idleness of this group of patients was attributed by themselves largely to their postgastrectomy symptoms.

DISCUSSION

The segmental operation described here was designed to minimize anatomic and functional disturbance of the stomach. Ulcer was to be treated simply by removing a large part of the acid-secreting mucosa, leaving all else intact, including the duodenum with its ulcer, the antrum, the pylorus, and the vagus nerves. A trial of this operation seemed to be justified by the results of animal experiments,[2] and by clinical experience with another version of segmental resection,[6] as well as by the apparently rational prospect that postoperative symptoms might be reduced. Although in this last respect there is now seen to be little to choose between the two operations, the results to date do indicate that retention of the innervated antrum, in its normal place in the gastrointestinal stream, along with the ulcer itself, does not predispose to a high rate of recurrence when the acid-peptic factor is sufficiently reduced.

It appears that postoperative symptoms in the present study are as closely related to the amount of stomach resected as to any other factor, but the similarity of results with the different operations studied here probably depends on a balance of those factors affecting both recurrence rate and symptoms. Retention of the antral secretory mechanism is probably compensated by a smaller parietal cell area than remains after the Billroth II operation, and by exposure of the antral and duodenal mucosae to the inhibitory influence of acid. Anatomically the antrum makes up in reservoir capacity for the greater loss of fundus by segmental resection. In the Billroth II operation, there is more acid-secreting mucosa, but the secretory mechanisms have been largely removed.

The necessity of dividing all the short gastric vessels was affirmed by the persistence of a duodenal ulcer and its symptoms in one patient in whom three of these vessels were left at the time of segmental resection. Another resection was required several months later. The pouch measurements, apparently of average size in this case, give only a rough idea at best of the amount of stomach remaining. The greater curvature is appreciably lengthened by the division of each short gastric vessel, and pouch measurements are hopelessly incorrect

unless all the vessels are divided. In dogs similarly it was necessary to avoid leaving more than 10 to 20 per cent of the stomach as fundic pouch in order to protect against histamine-induced ulcer.[2]

Substernal pain after gastrectomy suggests the occurrence of esophagitis due to regurgitation of gastric contents. Contributing factors may be the smaller gastric reservoir and straightening of the cardioesophageal angle, which occurs more noticeably in the segmental operation, due to division of all short gastric vessels. The normal action of the innervated antrum and pylorus in regulating gastric emptying probably also adds to the amount of esophageal reflux in conjunction with the small reservoir. Small hiatal hernias probably should be sought out and repaired with any type of gastrectomy, even though they were not previously noticed.

The segmental operation has the technical advantage of avoiding dissection of the duodenum, and, where that is a serious problem due to the extent or location of the ulcer, this procedure may be wisely chosen. The present series affords no evidence on this point since there were no complications related to the duodenal stump.

The final evaluation of apparently equally acceptable operations for ulcer can scarcely be made on the basis of comparing series of patients operated upon in different hospitals. Variables uncontrolled in such comparisons include the hospital populations, subjective judgments concerning indications for surgery and operability, operative technique including methods of estimating the size of resection, and interpretations of postoperative follow-up data. It seems evident that such variables can be minimized only by the principle of randomization and the double-blind technique in follow-up.

SUMMARY

A segmental gastrectomy in which innervation of the antrum and pylorus was preserved was compared, in part by double-blind technique, with a standard Billroth II type of gastrectomy in 295 male patients with duodenal ulcer. Operative mortality, recurrence of ulcer, and postgastrectomy symptoms at 1 to 5 years were similar in the two groups. There was a slightly greater frequency of substernal pain in the segmental group, and of palpitation and sweating in the Billroth II group, and there was more serious weight loss in the latter group.

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THE LATE DEVELOPMENT OF GASTRIC CANCER AFTER GASTRECTOMY FOR MALIGNANT DISEASE

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CARCINOMA occasionally occurs in the gastric remnant following subtotal gastrectomy and in the stomach which has been subjected to gastroenterostomy. This is hardly surprising since carcinoma of the stomach is one of the commonest of gastrointestinal malignancies. It would be significant if it could be shown that the gastric remnant or a stomach with a gastroenterostomy were sites of increased incidence of malignancy.

At one time carcinoma occurring under such circumstances was considered to be a great rarity. Indeed one writer (Wolfsohn, 1927[21]), after examining 1,200 gastroenterostomies without encountering a single instance of carcinoma, concluded that a carcinoma-inhibiting substance was possibly elaborated at the gastroenterostomy site. More recently an ever-increasing number of reports have described cases of carcinoma occurring either in the gastric remnant or in stomachs with gastroenterostomies.[6, 10, 14] Some of these reports have implied that there may be a causal relationship between the antecedent surgery and the carcinoma. The validity of such a conjecture at present is devoid of statistical proof. Experimental evidence is also lacking. The most that can be said is that carcinoma of the gastric stump occurs with sufficient frequency to warrant a high index of suspicion in the presence of suggestive findings.

Carcinoma of the stump or stomal site following gastrectomy for malignant lesions poses a somewhat different problem. Here recurrence must be differentiated from a second primary malignancy. Prolonged survival in itself following gastrectomy for malignant disease is a distressingly infrequent phenomenon. Prolonged survival with the development of a second malignancy at the stoma is rare enough to warrant recording. Pack[17] recorded one case following subtotal gastrectomy for reticulum cell sarcoma in the distal segment. Other isolated case reports of similar nature have been made by Plenk,[20] de Vernejoul,[4] Gould,[7] Peujniez,[19] Nicolaysen,[15] Stoloff and Lattimore,[25] and Steffensen.[23] In all of these the time interval following the original surgery for neoplasm was at least 7 years before the appearance of the second neoplasm. In most of them the time interval was even greater.

In the cases to be reported here the time intervals between the original resection for malignancy and the second resection for carcinoma of the stump were 23 and 32 years, respectively.

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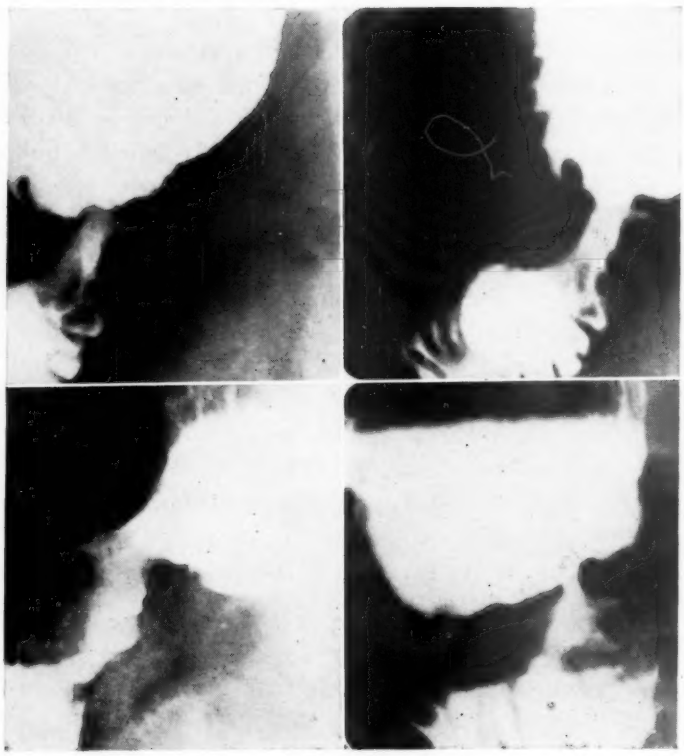
A.



B.

Fig. 1.—Case 1. *A*, Radiograph showing recurrent lesion in gastric stump. *B*, Spot films of same. *C*, Postoperative film.

CASE REPORTS

CASE 1.—J. H., a 75-year-old white man, entered the hospital with the complaints of a 30 pound weight loss, anorexia, and postprandial epigastric distress, all of approximately 3 months' duration. These symptoms had been growing progressively more severe over a 3-month period. There had been no nausea, vomiting, hematemesis, or melena.

The patient gave a history of having had a carcinoma of the stomach resected 23 years prior to admission. This was confirmed by obtaining not only the report, but also by having the slides reviewed and the diagnosis confirmed (adenocarcinoma, stomach). There was no evidence of lymph node invasion at the time of the previous surgery.

The systemic review was negative.

On physical examination the temperature was 98.6° F., the blood pressure 136/70, and the weight 129 pounds.

The positive findings were limited to the abdomen. There was a healed left paramedian incision. No discrete abdominal masses were palpable. The liver was not felt. The rectal examination was negative.

Laboratory work revealed hemoglobin of 12 Gm., and hematocrit of 40. The white blood cell count was 7,000 with 61 per cent polymorphonuclear cells. The urine was negative. The alkaline phosphatase was 2.3 Bodansky units. The liver function tests were uniformly negative aside from a bromsulphalein retention of 18 per cent. The serum albumin was 4 Gm. per cent, and the serum globulin 2 Gm. per cent.

C.

Fig. 1 (Cont'd).—For legend see opposite page.

Gastric analysis revealed achlorhydria. There was no occult blood in the stool.

X-ray examination (Fig. 1) revealed approximately 20 per cent of stomach remaining. The distal 4 cm. of the gastric pouch was markedly constricted in a concentric manner with effacement of the normal mucosal pattern at the site of constriction. There was a small triangular projection (0.5 cm.) extending from the lesser curvature aspect of the mid-portion of the zone of constriction. The x-rays were interpreted as most likely representing a recurrent or primary malignancy.

Operation (Dr. Louis Sperling).—At operation there was found an indurated mass at the site of the previous anastomosis (retrocolic gastrojejunostomy), obviously neoplastic in nature. There was marked dilatation of the afferent loop which was obstructed at the anastomotic site. There were several palpable lymph nodes in the small bowel mesentery near the anastomotic site. There were no other palpable nodes. There were no gross hepatic metastases.

A re-resection of the gastrojejunostomy including 15.5 cm. of the efferent loop, 5.5 cm. of the afferent loop, and approximately one-half of the remaining stomach was performed. The line of resection was at least 2 to 2.5 cm. from the gross tumor. A Billroth I type of reconstitution was performed following re-anastomosis of the jejunum near the ligament of Treitz.

The postoperative course was entirely uneventful.

The pathologic specimen revealed an extensive adenocarcinoma invading the distal stomach and involving the entire gastrojejunostomy site. Microscopically, the tumor showed papillary as well as undifferentiated features (Fig. 2). There were metastases to regional lymph nodes, as well as extensive intramural lymphatic invasion. There was extension to the serosa and subperitoneal fibrofatty tissue. Microscopically tumor was seen to be infiltrating to the line of resection although none had been seen here grossly.

Postoperatively the patient did well for about 6 months. He gained weight and enjoyed relatively good health. Thereafter, there was onset of anorexia, weight loss, and postprandial epigastric distress.

A re-exploration performed in July, 1959, revealed metastatic disease involving the liver as well as extensive local recurrence. The patient is now preterminal.

CASE 2.—B. A., a 69-year-old white woman, entered the hospital with the complaints of postprandial epigastric discomfort and retrosternal burning. These symptoms had begun approximately 2 years prior to admission but had grown progressively worse. At the time of admission, there was rather severe upper abdominal "pressure" shortly after eating. This was particularly marked after the ingestion of raw fruits and vegetables, as well as meat. There had been progressive anorexia and a 16 pound weight loss in 6 months. The only relief that the patient obtained was with the ingestion of buttermilk.

In the past history it was revealed that the patient had undergone a gastric resection 32 years prior to this admission. This had been done at an Eastern hospital. Duplicates of the operative as well as the pathology reports were obtained and revealed that the resection had been performed for a reticulum cell sarcoma of the distal portion of the stomach.

Physical examination revealed a chronically ill, pallid, white woman. The temperature was 98.2° F., the blood pressure was 150/90, and the weight 142 pounds. The positive findings were limited to the abdomen, where there was present a large ventral hernia. There was slight epigastric tenderness, as well as tenderness in the right upper quadrant and right lower quadrant. There was marked pigmentation of the anterior abdominal wall where the patient had received postoperative radiation therapy. The rectal examination was negative.

The preoperative hemoglobin was 12.5 Gm. per cent, the hematocrit 40, and the white blood cell count was not remarkable. X-rays (Fig. 3, *A*) revealed no definite lesion at the site of gastrojejunostomy nor any intrinsic gastric lesion. However, there appeared to be a prolonged spasm at the efferent limb, indicating some disturbance in the emptying mechanism of the residual stomach. Also revealed on the x-rays taken at this time was a large solitary calculus in the gall bladder. The patient was subjected to laparotomy.

Operation.—At the site of the gastrojejunostomy, particularly in the region of the afferent limb, there was an indurated mass measuring approximately 5 by 3 by 2 cm. This was very hard and to the examiner felt very suspicious of neoplasm. A small gastrotomy incision was made. A small portion of the indurated area was taken for biopsy and given to the pathologist who reported this as showing adenocarcinoma. Accordingly, a re-resection of the gastrojejunostomy site, including at least 12 cm. of the afferent and efferent limbs of the jejunum and approximately 50 per cent of the remaining gastric remnant, was performed. It was felt that the tumor had been cleared by approximately 3 to 4 cm. There were no palpable lymph nodes nor was there any gross evidence of hepatic metastasis.

Following re-anastomosis of the jejunum near the ligament of Treitz, a Billroth II type of reconstitution of the gastrojejunostomy was performed. The postoperative course was relatively uneventful, and the patient left the hospital on the twelfth postoperative day.

At this time, 18 months after surgery, the patient is eating comfortably and maintaining her weight. A recent x-ray study of the gastric remnant failed to reveal recurrent neoplasm (Fig. 3, *B*). There is no evidence of distal metastatic disease.

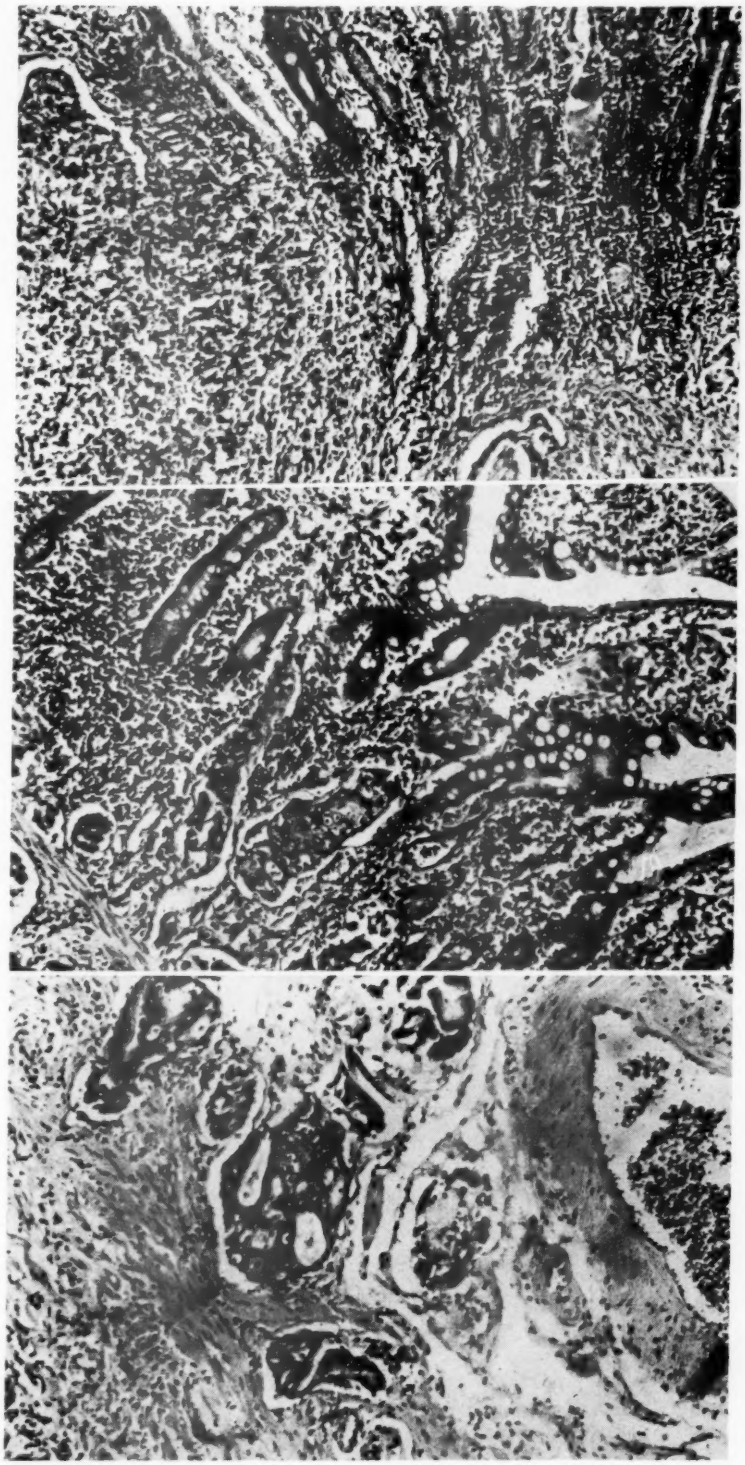
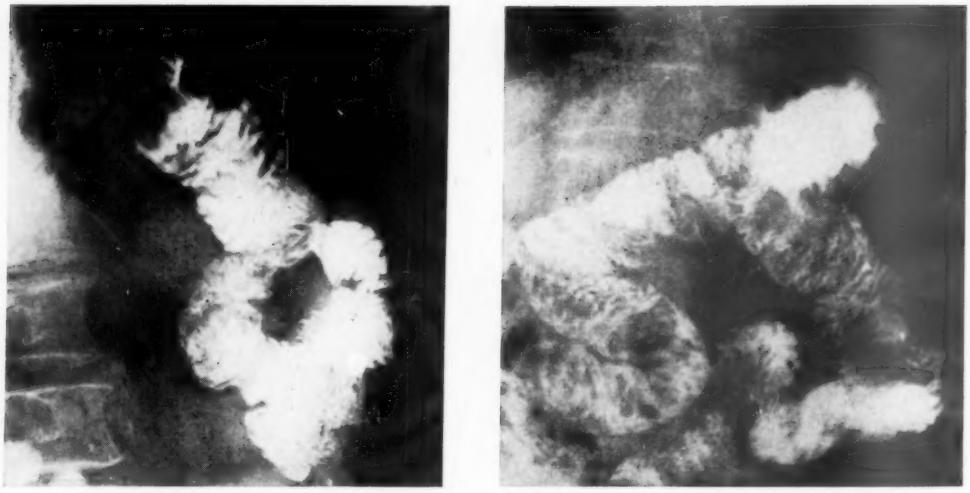


Fig. 2.—Case 1. *A*, Undifferentiated carcinoma on stomach side. *B*, Invasion of jejunal portion of stoma. *C*, Lymphatic invasion.

DISCUSSION

Carcinoma of the gastric stump when it occurs usually develops in the vicinity of the gastrojejunostomy site. In Pack's series,[18] close to 70 per cent were in the neighborhood of the stoma. This might lead to speculation that some etiological relationship exists between factors operative at the stoma and subsequent neoplasia. This, of course, is most difficult to prove. It is well known that both acute and chronic inflammatory changes may be found in the vicinity of the gastroenterostomy. But these are generally found early, not late. Even if it were a constant finding, the causal relationship would still be hypothetical. Another hypothetical factor which could be implicated is the constant bathing of the stomal site with biliary and pancreatic secretions. Again, an etiological relationship is impossible to prove or disprove but appears unlikely.



A. *B.*

Fig. 3.—Case 2. *A*, Preoperative radiograph showing no definite lesion. *B*, Postoperative radiograph.

In cases of carcinoma occurring late after subtotal gastrectomy for malignancy, the problem of differentiating recurrence from a new malignancy is a real one. When the two lesions are of different histologic types—for example, reticulum cell sarcoma followed by adenocarcinoma—there is little question that the second lesion is a new primary. However, when the tumor is of the same histologic nature, only the time factor militates against the diagnosis of recurrence. This, of course, is not an absolute criterion. It is well known that the host resistance of some patients to tumor is such that they may live many years with a malignancy in a kind of "peaceful coexistence." Nevertheless, it is true that in gastric cancer the majority of recurrences occur within a 3-year period. Of these recurrences the number occurring in the stump varies in the literature from as low as 19.6 per cent (Warren) to as high as 50 per cent (McNeer[12]).

Are long-term survivors of resected gastric cancer more prone to gastric stump cancer than those having resections for other causes? To determine this,

one would have to compare the incidence in the benign group with that in long-term survivors from gastric cancer. In both groups one would have to compare such figures with the over-all expected incidence, taking into consideration that more than one-half of the stomach that could form tumor is now absent.

The statistical problem thus becomes one of immense complexity. It would appear that in patients gastrectomized for benign disease the incidence of late

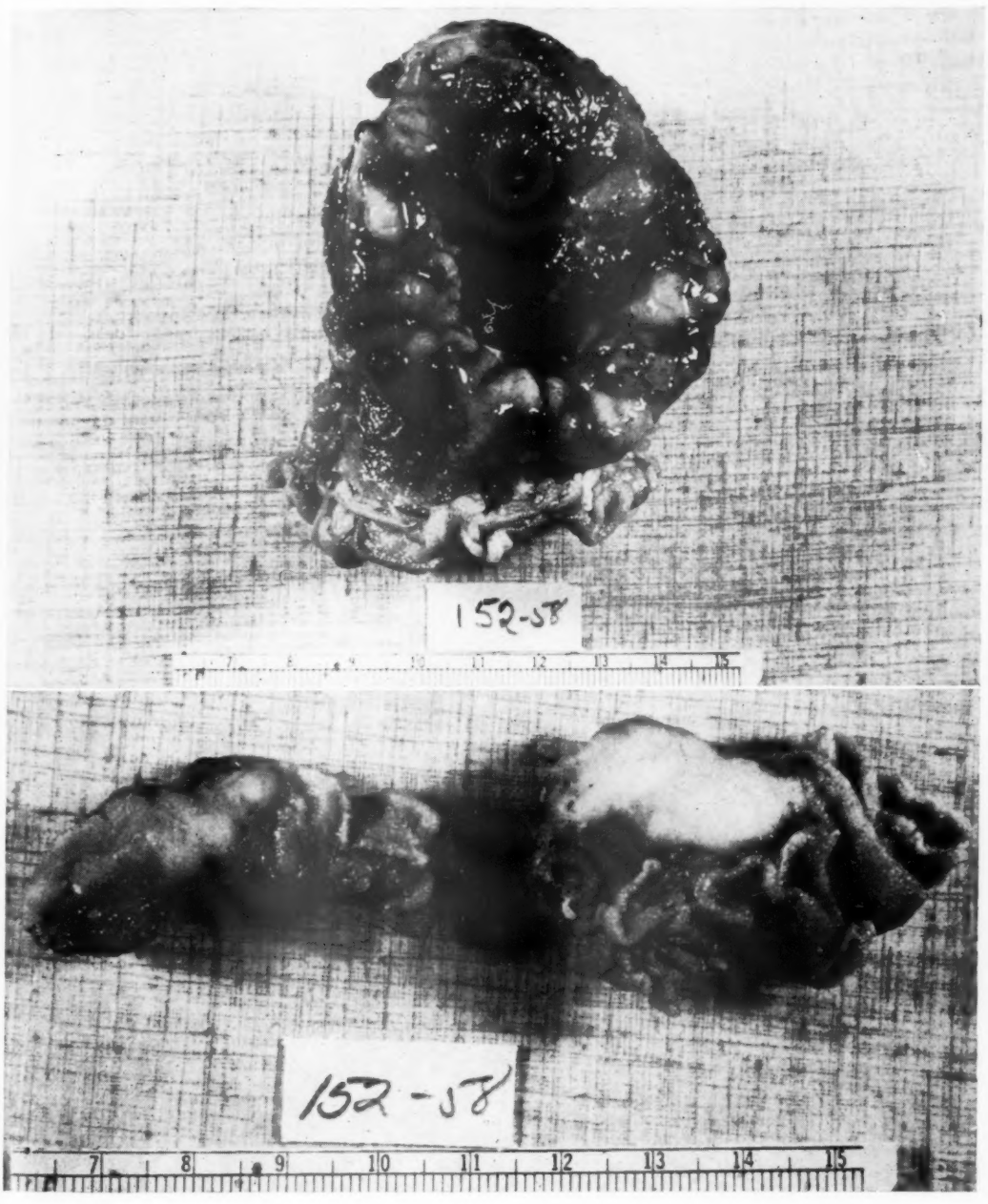
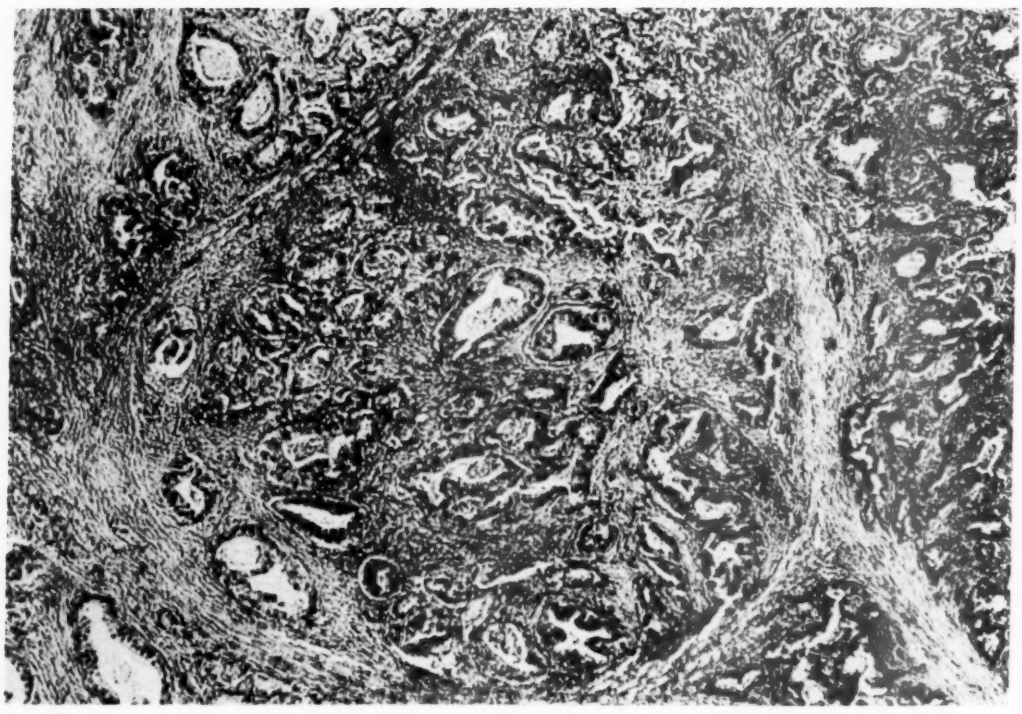


Fig. 4.—Case 2. *A*, Gross view of resected specimen showing carcinoma (superior margin). *B*, Cross section of same.

A.



B.

Fig. 5.—Case 2. *A*, Low-power photomicrograph of tumor involving stoma. *B*, High-power photomicrograph of carcinoma.

carcinoma is about 1 per cent. In the general population the death rate for malignant neoplasm of the stomach is 13.2 per 100,000.[27] Cancer of the stomach comprises 2.3 per cent of all necropsies and 15.0 per cent of all tumors.[24] In two well-known clinics, the admission rate for this disease was one in every 200 to 265 patients.[5] The occurrence of this lesion (carcinoma of the stump) is most probably coincidental. This opinion is at variance with the opinion

TABLE I

AUTHOR AND YEAR OF REPORT	PRIMARY OPERATION AND PATHOLOGIC DIAGNOSIS	INTERVAL PRECEDING RE-RESECTION	SECONDARY OPERATION, PATHOLOGIC DIAGNOSIS AND SITE	RESULTS
Walters, Gray, and Priestley, 1942	Subtotal gastrectomy (Billroth I) Adenocarcinoma Grade IV	11½ years	Re-resection Colloid carcinoma Grade III	Died 14 months
Brunschwig, 1947	Subtotal gastrectomy (Polya) Carcinoma	9½ years	Resection gastric remnant, 1 over esophagus, spleen, tail of pancreas, and transverse colon Adenocarcinoma	Died 7 months
Patterson (reported by McNeer, 1950)	Subtotal gastrectomy (Polya) Adenocarcinoma	13 years, 10 months	Resection gastric remnant Carcinoma	Died 7 months
McNeer, 1950	Subtotal gastrectomy (Hofmeister) Reticulum cell sarcoma	6 years, 8 months	Re-resection Adenocarcinoma	Died 1 year following surgery
de Vernejoul, 1951	Subtotal gastrectomy Carcinoma	7 years	Total gastrectomy	No follow-up reported
Plenk, 1955	Subtotal gastrectomy Carcinoma	15 years	Total gastrectomy	No follow-up reported
Stoloff and Lattimore, 1955	(1) Subtotal gastrectomy (Billroth II) Adenocarcinoma	12 years	Re-resection Adenocarcinoma	7 years symptom free, living (age 79) at time of report (6 months post-operation)
	(2) Recurrence of (1)	7 years	Resection of remaining remnant Medullary carcinoma	
Nicolaysen and Llavaag, 1956	"Gastric cancer"	15 years	Re-resection Carcinoma	No follow-up reported
		25 years	Re-resection Carcinoma	
		39 years	Re-resection Carcinoma	
Steffensen, 1957	Subtotal gastrectomy (Polya) Carcinoma	24 years	Re-resection Mucinous carcinoma	Died 6 months
Morgenstern, 1959	(1) Subtotal gastrectomy (Polya) Adenocarcinoma	23 years	Re-resection	Dying of recurrence after 12 months
	(2) Subtotal gastrectomy (Polya) Reticulum cell sarcoma	32 years	Re-resection	Living and well 18 months post-operation

expressed by Helsingen and Hillestad,[10] who find that in cases resected for gastric ulcer the incidence of gastric stump carcinoma is three times that expected to occur in the normal population.

The information we have at hand in malignant lesions is much too sparse to be of statistical validity. The number of long-term survivors is low to begin with. The number of cases which develop a late malignancy amounts to a very small number. The two groups, therefore, cannot be compared statistically nor can any valid conclusion be drawn as yet.

Knowing that stomal carcinoma can and does occur, how does this help us in evaluating the problem cases as represented by the two cases reported here? The diagnosis of carcinoma of the stump is made correctly only rarely. In many cases the patients are treated for a benign lesion, such as marginal ulcer, only to succumb to a lethal malignant tumor. The lesion must be kept in mind in the presence of any ulceration or deformity involving the stoma occurring late after gastrectomy.

The salvage rate in carcinoma of the gastric stump is low. Most of the patients are inoperable at the time the diagnosis is made. Of those in whom re-resection is feasible, the outlook is poor. Of 8 cases in which a follow-up is reported, the average survival time was less than one year (Table I).

However, it must be recognized that some of these patients may be made more comfortable for another 6, 12, or 18 months, perhaps longer. In the face of the obstructive symptomatology which a stomal tumor engenders, resection is a worthwhile palliative procedure. In some cases it may even result in cure. Stoloff and Lattimore[25] report the case of a 79-year-old man who underwent total gastrectomy for his third gastric carcinoma in 19 years, each treated by resection. At the time of the report he was eating and gaining weight.

SUMMARY

Carcinoma of the gastric stump occasionally occurs many years following resection for a primary malignancy. In this respect it does not differ from those cases reported following gastric resection for benign disease. No causal relationship is known to exist between previous resection and subsequent neoplasia. Ulceration or deformity of the gastroenteric stoma should alert one to the possibility of malignant tumor in this region. Re-resection is recommended as a palliative or definitive surgical procedure. Two cases of carcinoma of the gastric stump occurring 23 and 32 years following the primary resection are reported.

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CARDIOSPASM FOLLOWING VAGOTOMY

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THERE have been few reports of cardiospasm following vagotomy in the literature. There has been only one such report following subdiaphragmatic vagotomy. This has been in spite of the widespread acceptance of vagotomy as an adjunctive procedure in the surgical treatment of duodenal ulcer and the consequent use of this procedure in thousands of cases. One, then, would suspect that this is a relatively rare complication of subdiaphragmatic vagotomy. It is the purpose of this report to describe two cases and their management and to review the literature briefly.

CASE REPORTS

CASE 1.—Mrs. F. P., a 33-year-old white housewife, had been treated for duodenal ulcer with a Sippy type of management without relief of symptoms for 2 years. She had never had hematemesis or melena, but, because of intractable pain and roentgenographic evidence of continued activity and crater, operation was advised.

On March 18, 1958, a 50 per cent gastrectomy and subdiaphragmatic vagotomy were performed. The anastomosis was an antecolic Hofmeister type of gastrojejunostomy. A complementary gastrostomy was carried out, and at no time did the patient have an indwelling nasogastric tube. On the third postoperative day fluids were begun orally, and the patient rapidly advanced to a bland diet. She had diarrhea common to postvagotomy patients from the fourth to the sixth postoperative days. She was discharged on the eighth postoperative day. On April 21, 1958, 34 days after surgery the patient was seen complaining of inability to swallow. Barium swallow on that day (Fig. 1) revealed cardiospasm with only a trickle of barium going through the cardia. The narrowing of the esophagus was supradiaphragmatic. She was treated with tincture of belladonna orally and gradually improved over the ensuing 3 weeks until she was able to eat any food. During this period of time she lost 20 pounds. Since then the patient has done well. A follow-up gastrointestinal series on Nov. 11, 1958, revealed a normal esophagus and a normal stomal site.

CASE 2.—Mr. E. A. C., a 49-year-old white man, had had burning epigastric pain for approximately one year. The pain was worse when his stomach was empty, and it was partially relieved by milk, food, or antacids. He had had several episodes of vomiting, but he had not vomited blood. Gastrointestinal series revealed marked gastritis and duodenal deformity. Therapy consisting of a progressive Sippy-type diet, probanthine, antacids, and phenobarbital had been of no relief over a 4-month period, and surgical intervention was advised.

On Jan. 16, 1959, a 40 per cent gastric resection, subdiaphragmatic vagotomy, and complementary gastrostomy were performed. The anastomosis was an antecolic Hofmeister type of gastrojejunostomy. At no time did the patient have an indwelling nasogastric tube. The postoperative course was benign. The patient was placed on liquids on the third postoperative day and progressed to a bland diet on the sixth postoperative day. He was discharged on the ninth postoperative day.

On Jan. 29, 1959, 13 days after surgery the patient complained of food sticking in his chest. A barium swallow that day revealed marked contracture of the lower one-fifth of the esophagus. Treatment with nitroglycerine offered very little relief, and repeated barium swallows on Feb. 6 and 13, 1959 (Fig. 2) were unchanged. Accordingly, on February 13

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esophagoscopy was performed. At esophagoscopy no mucosal edema or luminal stenosis was seen. Dilatation of the cardia by balloon was accomplished. Following this the patient improved dramatically and has required no further therapy.

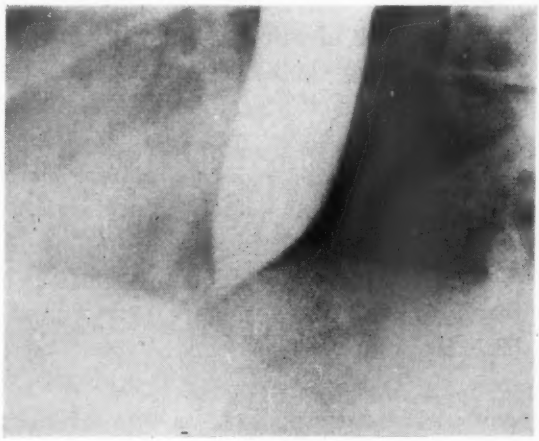

Fig. 1.—Case 1. Barium swallow 34 days following subdiaphragmatic vagotomy illustrating cardiospasm.

Fig. 2.—Case 2. Barium swallow 21 days following subdiaphragmatic vagotomy illustrating cardiospasm.

DISCUSSION

It has been shown by Houssay[3] and by Shay, Komarov, and Gruenstein,[7] and later by Donald[1] that infradiaphragmatic section of the vagi in rats results in dilatation of the lower esophagus associated with vomiting and retention of food in the dilated esophagus. Hwang, Essex, and Mann[4] have shown that in the dog vagotomy at the level of the lung hilus results in loss of peristalsis of the lower esophagus and a condition similar to cardiospasm or achalasia. Jefferson and associates,[5] working also with the dog, found that this effect could be

nullified by concomitant phrenicotomy. These workers also noted that low thoracic vagotomy had either no effect on the esophagus or resulted in transient cardiospasm. Many writers have suggested that cardiospasm might result following vagotomy in the human. According to Dragstedt[2] a true case of cardiospasm has not been encountered in some 1,500 vagotomies performed at that clinic. He says that transient dysphagia occurs occasionally which clears in a matter of 3 to 4 weeks and is attributable to edema and/or trauma incident to the operative procedure. He further states that what may be thought to be cardiospasm more likely is stenosis of the lower esophagus following the healing of peptic esophagitis or of a lower esophageal peptic ulcer.

Wilcox[9] has reported a case of cardiospasm following subdiaphragmatic vagotomy done as the total therapy for duodenal ulcer in a 55-year-old man. Inability to swallow began on the ninth postoperative day and barium swallow confirmed cardiospasm. He was esophagoscoped and dilated and 11 days later was able to eat.

Moses[6] reported a case of cardiospasm following supradiaphragmatic vagotomy which was treated by celiac ganglion block. Hoeder and Delcourt[8] report the case of a patient who had a bilateral transthoracic vagotomy and developed prolonged and severe dysphagia 12 days postoperatively. Esophagoscopic examination in this case revealed the narrowing to be due to edema.

Cardiospasm and stenosis of the lower esophagus following subdiaphragmatic vagotomy is not easily explained, and in Case 1 would be particularly difficult to explain since the symptomatology did not begin until the thirty-fourth postoperative day. This may well be due to sympathetic-parasympathetic nerve imbalance as suggested by Wilcox rather than the result of local edema. This appears to be a self-limited condition, but it required esophageal dilatation in one of our cases.

SUMMARY

Two cases of cardiospasm following subdiaphragmatic vagotomy and subtotal gastric resection are reported. The pertinent literature is reviewed. This appears to be a rarely seen, self-limiting complication which may require esophageal dilatation for relief.

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MEASUREMENT OF ACUTE PORTAL OBSTRUCTION BY CLEARANCE OF RADIOACTIVE SODIUM FROM THE COLON

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THE portal circulation is a unique vascular system originating and terminating in a capillary bed and being subject to variable anastomotic communications dependent on species difference or disease. Quantitative assessment of portal flow is at best difficult because of remoteness of the major portion of the system from easy observation; and because of complex transient or permanent changes which occur not only in diseased states, but also under normal circumstances.

A method to evaluate the portal circulation would be to measure the clearance or "drainage" of material from the wall of the gastrointestinal tract. Here the sole source of outflow is the portal system and lymphatics. Kety[1] has shown that clearance of a radioisotope from a tissue is a measure of the local circulation. This study attempts to: (1) determine the type of clearance rate curves obtained from injection of radioisotope into the submucosa of the colon, (2) observe the effect of acute portal occlusion on these rate curves, and (3) ascertain the influence of other vascular phenomena on the changes seen in the rate curves of clearance.

METHOD

Mongrel dogs of both sexes weighing between 5 and 12 Kg. were used. All experiments were performed under intravenous Nembutal and endotracheal anesthesia. Initially, in all instances, a femoral artery was cannulated and a continuous arterial pressure was recorded by strain-gauge manometer. A midline celiotomy incision was then performed and a medium-sized tributary of the portal system was cannulated in the base of the small bowel mesentery, and a continuous portal pressure was recorded utilizing a special low pressure transducer. The colon was then delivered into the operative field and fixed at a point approximately 10 inches from the anus by a rigid brass rod which was

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passed through the mesocolon, between the colon and its marginal artery. A colotomy was performed along the antimesenteric border and the edges of the colon were allowed to gape thus exposing the mucosa.

Submucosal injection of 0.1 ml. of a solution of saline containing 5 microcuries of radioactive sodium (Na^{22}) was performed utilizing a Hamilton microsyringe and a No. 26 needle. This raised a visible bleb in the mucosa. The surface of the mucosa was flushed with saline and gently blotted with a sponge to ensure that all the radioactivity measured was submucosal. A mica end window geiger counter (Nuclear-Chicago) with a 1 cm. diameter window was positioned 1 cm. above the bleb and rigidly fastened to the brass rod supporting the exposed mucosa so that movements of the animals would not disturb bleb-to-detector geometry.

The geiger counter was connected to a recording scaler and a recording ratemeter. The recording ratemeter provided an immediately observable clearance curve. For more precise calculation of clearance rates the data provided by the recording scaler (counts collected each minute) were plotted by hand on semilog graph paper from which the clearance rate constant (K) and any deviation from a pure exponential form could be readily determined.

Three groups of animals were used. In the first group, 4 dogs were utilized in the manner described to obtain the normal or control curves of clearance from the colon submucosa. In the second group, conditions were similar to the first group, but in these 5 animals the portal vein proximal to the liver was acutely occluded with a Blalock clamp. Immediately following occlusion the isotope was injected. Duration of occlusion was 10 to 20 minutes. Following release of the occlusion, the measurement of clearance was continued for 20 to 30 minutes.

The third group, consisting of 3 animals, was tested in a manner similar to the second group, but here blood transfusion was administered (250 ml.) by means of a femoral vein canula during the 10- to 15-minute period when the portal vein was occluded. This was done to circumvent the arterial hypotension which occurred with acute portal obstruction. During the experiments entailing occlusion of the portal vein, biopsies of the colon near the site of injection were performed. These were carried out before obstruction and at intervals thereafter.

RESULTS

In group one (Fig. 1) where the portal vein was not disturbed the rates of disappearance were single exponential curves with a K or rate of clearance of 6.3, 7.1, 7.3, and 7.3 per cent per minute. After 20 to 25 minutes, the rate of clearance slowed. No reason for this occurrence was evident. The arterial and portal pressures remained constant throughout the experiment (Inset Fig. 1).

In group two (Fig. 2) acute occlusion of the portal vein was characterized by either no clearance or apparent reversal of clearance of the isotope. With release of the occlusion, clearance readily occurred at rates (K) of 6.3 to 13.9 per cent per minute. During occlusion the portal pressure rose from 160-200 mm. to 370-480 mm. saline. The arterial blood pressure declined from levels of

systolic 135-160 and 80-100 diastolic to 50-70 systolic and 25-35 diastolic (mm. Hg). Pressure promptly returned to the approximate preocclusion values with release of the occluding clamp (Inset Fig. 2).

In group three (Fig. 3) the experiments of group two were repeated except for rapid blood transfusions which were administered during portal occlusion and which maintained the arterial blood pressure between 95-115 systolic and

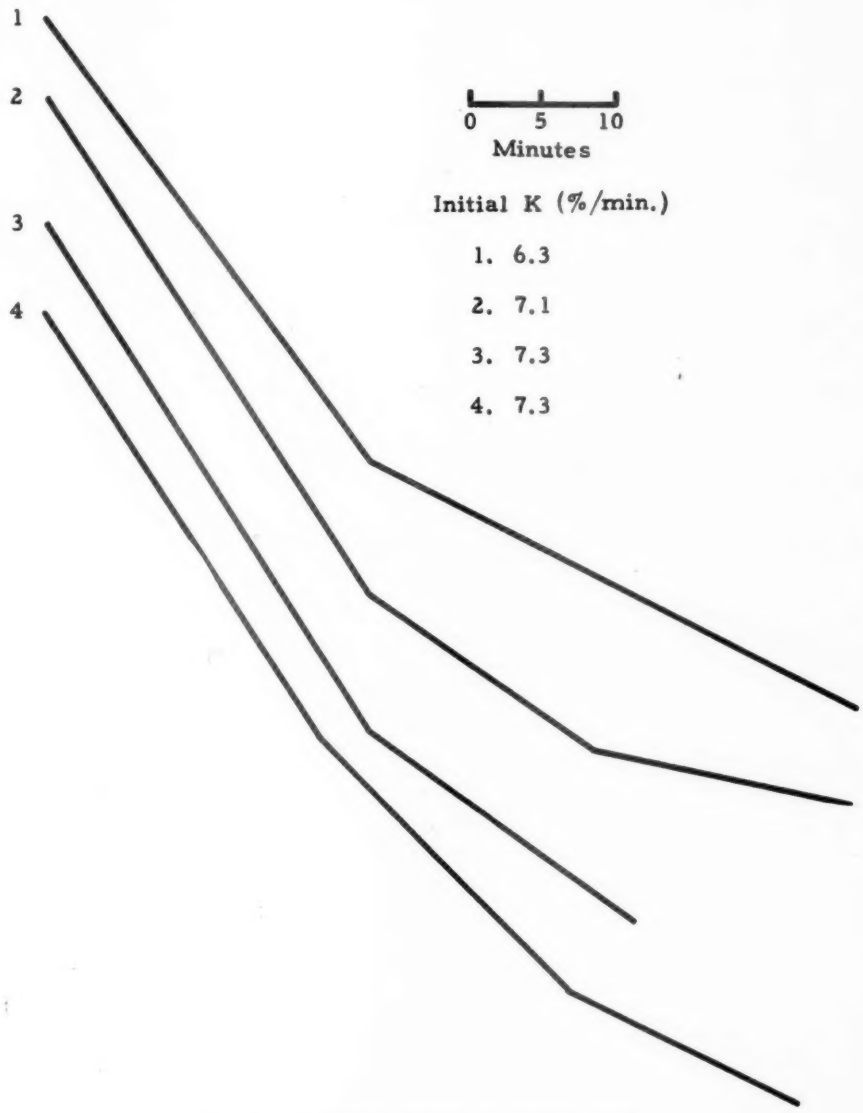

Fig. 1.—Clearance curves in control dogs.

50-65 diastolic (mm. Hg). The portal pressures during occlusion rose to 420-550 mm. saline. In these animals, which remained relatively normotensive by virtue of massive blood replacement, initial transient clearance was followed by no clearance until the occlusion was released (Inset Fig. 3).

Histologic examination of the colon biopsies obtained in the experiments entailing portal obstruction (with and without transfusion) uniformly showed

marked congestion and even areas of hemorrhage in the bowel wall. This was most marked in the submucosa although the other layers were at times also involved.

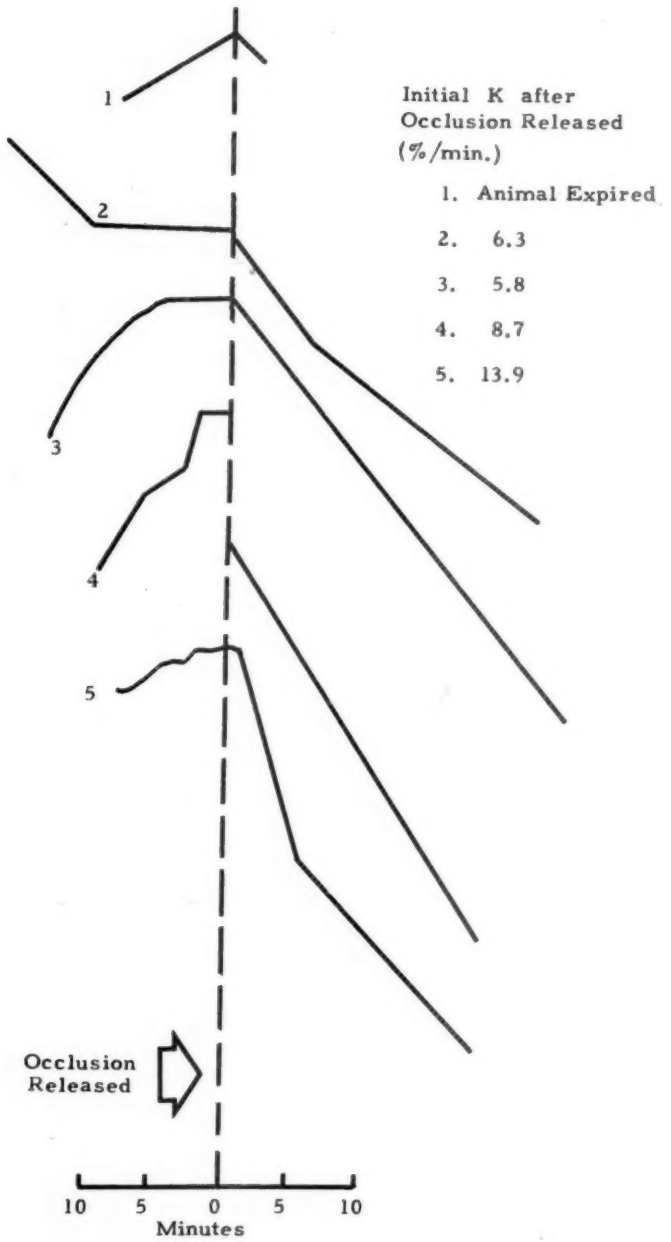

Fig. 2.—Clearance curves in dogs with portal veins completely occluded.

DISCUSSION

The clearance of radiosodium (Na^{22}) from the submucosa of the colon was first observed in order to determine the type of curve which could be obtained. A single exponential line as plotted on semilog graph paper could be drawn in

animals with an undisturbed portal system and whose arterial blood pressure remained unchanged. This clearance or K for the colon is in accord with Kety's demonstration of the clearance of radioisotope as an index of local tissue circulation. A break in the clearance curve occurred after 20 to 25 minutes. No apparent reason for this was evident although at this interval most of the injected

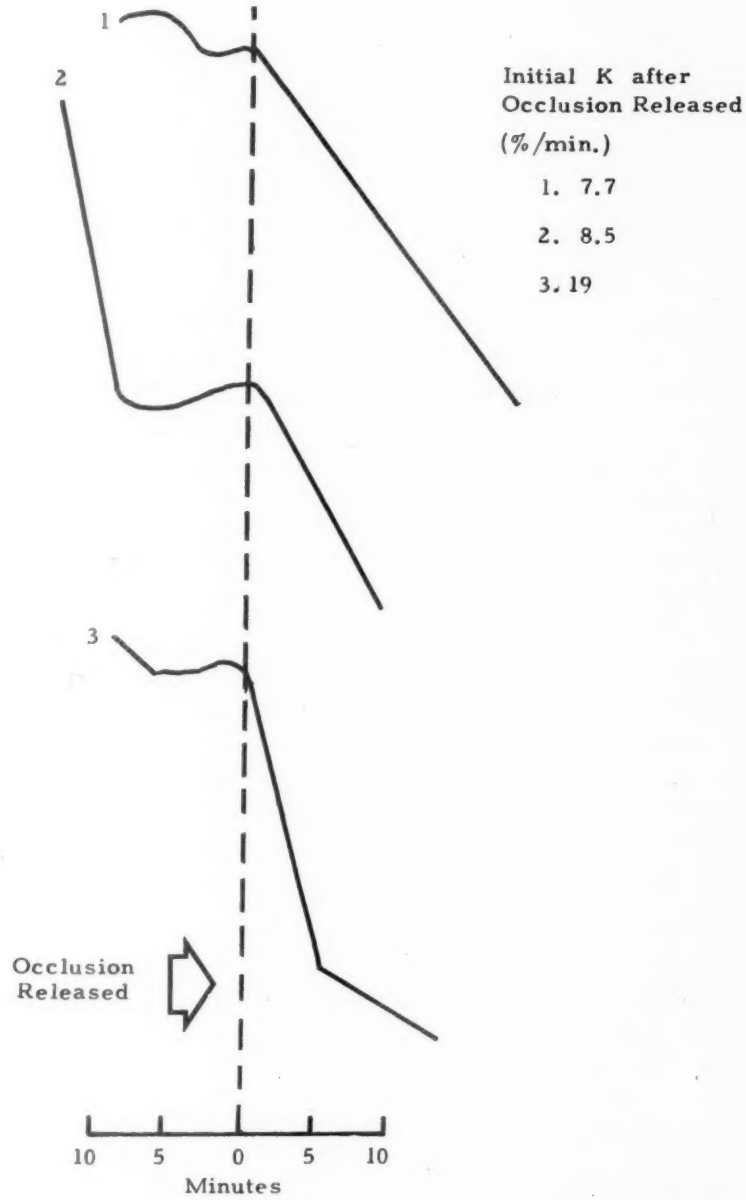

Fig. 3.—Clearance curves in transfused dogs with portal veins completely occluded.

isotope was already cleared. The break in the control curves indicated, however, that the same injection could not be used as its own control prior to portal occlusion because the expected slowing of the disappearance rate would occur during the critical phase of the test.

Acute portal obstruction produced the expected elevation of the portal pressure and reduction of the arterial blood pressure. The bowel mucosa became engorged and turgid and small mesenteric hemorrhages were evident after only 10 minutes of occlusion.

When radiosodium (Na^{22}) was injected at this time into the submucosa, not only did the isotope fail to clear, but there was actually a build-up or increase of counting rate. A possible explanation for this would be that the increased venous pressure and concomitant decreased arterial pressure resulted in marked reduction or even disappearance of the arterioportovenous pressure gradient. During this event retrograde venous flow carrying the isotope more superficially and thus closer to the detector might have occurred.

Transfusion during occlusion maintained arterial pressure and thereby produced a gradient closer to the normal value. At this time a transient initial clearance occurred which was followed by no clearance, but there was no appreciable build-up or increase in counting rate.

Tissue clearance tests measure the effective blood inflow to and outflow from the site of injection. When lack of clearance followed acute portal obstruction, it was necessary to rule out the role of arterial hypotension as a cause for this occurrence. Transfusion during portal occlusion maintained a normal blood pressure. No clearance of isotope at this time apparently signified that acute portal outflow obstruction alone could produce this effect.

The rate of clearance after release of portal occlusion was comparable to or greater than the control values. The highest rate of 19 per cent per minute occurred in one of the transfused animals. The increase in clearance observed in some of the animals after release of occlusion resembles the reactive hyperemia reported by others[2] in clearance from muscle.

Histologic studies indicated that tissue damage in the form of small hemorrhages occurred mainly in the submucosa in all instances where the portal vein was occluded for 10 or more minutes. This, however, did not alter the clearance of radiosodium (Na^{22}) following release of portal occlusion.

In conclusion, it may be said that measurement of acute portal outflow obstruction by clearance of radiosodium (Na^{22}) from the colon submucosa of dogs is feasible.

SUMMARY

The clearance of radiosodium (Na^{22}) from the colon submucosa of dogs was used as a measure of acute portal obstruction. Consistent clearance constants (K) are obtainable when the portal system is left intact. When acute portal occlusion is produced no clearance occurs even when the arterial hypotension which accompanies portal occlusion is circumvented by blood transfusion.

We are grateful to Dr. John J. Farrell, Chairman, Department of Surgery, University of Miami School of Medicine, for his critical review of this report.

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A NEW METHOD OF PANCREATICODUODENECTOMY DESIGNED TO PRESERVE LIVER AND PANCREATIC FUNCTION

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PANCREATICODUODENECTOMY is now the generally accepted treatment for carcinoma of the pancreatic head, lower portion of the common bile duct and duodenum, and in instances in which stomach tumors have infiltrated into the head of the pancreas and duodenum. However, the operative mortality after this procedure is high and the long-term survival rate is low. This is partly due to the many technical difficulties accompanying the operation. The more important difficulties occur at the following sites: (1) the portal vein and superior mesenteric vessels, (2) the pancreaticojejunostomy, and (3) the choledochojejunostomy.

In my experience, there have been only a few cases in which it was necessary to create a portacaval shunt or to resect the superior mesenteric vessels. When these vessels have been invaded, metastases are usually found in the porta hepatis or retropeitoneally and resection is not indicated. This contradicts the report of Hubbard[3] who has reported low recurrence of tumor following portal vein resection. This paper deals with the problems encountered at the sites of pancreaticojejunostomy and choledochojejunostomy and experimental work designed to overcome these difficulties.

PANCREATICOJEJUNAL ANASTOMOSIS

Our clinical and experimental results in pancreatic resections have shown that the preservation of internal and external secretions of this organ are essential for long-term survivals. To ensure continued external secretion, a pancreaticojejunal anastomosis is necessary. The anastomosis between the pancreatic stump and jejunum is generally accomplished in two ways: (1) implantation of the pancreatic stump into the jejunum, (2) mucosa-to-mucosa anastomosis between jejunum and pancreatic duct. Table I shows that suture line breakdown occurs five times more frequently in dogs using implantation as compared to the mucosa-to-mucosa anastomosis. In long-term survivors, obstruction of the pancreatic duct occurred in almost all cases in the former while the latter did

TABLE I. THE INCIDENCE OF ANASTOMOTIC BREAKDOWN IN DIFFERENT PANCREATOJEJUNAL ANASTOMOSES

	SUTURE LINE BREAKDOWN
Implantation of pancreatic stump into jejunum	71% (10/14)
Mucosa-to-mucosa pancreatojejunal anastomoses	13% (2/15)

Paper received from Dr. George E. Moore, Roswell Memorial Park Institute, Buffalo, N. Y.
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not show this complication. Microscopically, the pancreatic lobules, zymogen granules, and ducts are intact in those with the mucosa-to-mucosa anastomosis, while in the implantation group there is atrophy of the glandular cells; the lobules and zymogen granules cannot be recognized* (Figs. 1 and 2).

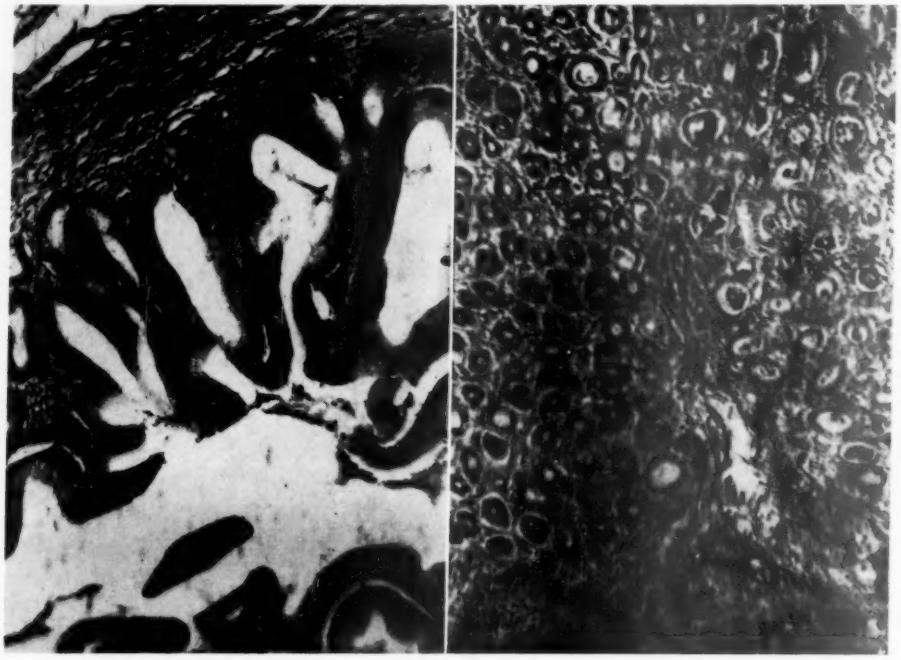


Fig. 1. Fig. 2.

Fig. 1.—Photograph showing preservation of normal pancreatic architecture following mucosa-to-mucosa anastomoses.

Fig. 2.—Photograph showing pancreatic atrophy after the implantation method.

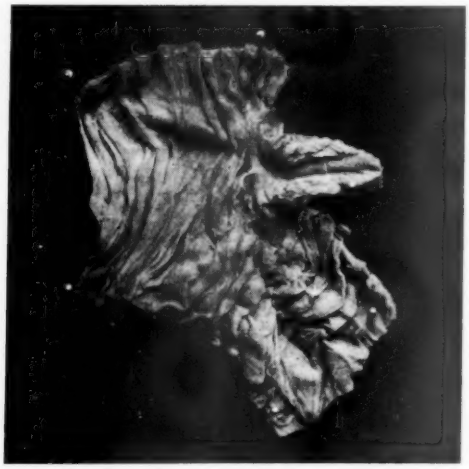


Fig. 3.—Autopsy specimen of a 44-year-old man showing patent pancreatojejunal anastomoses.

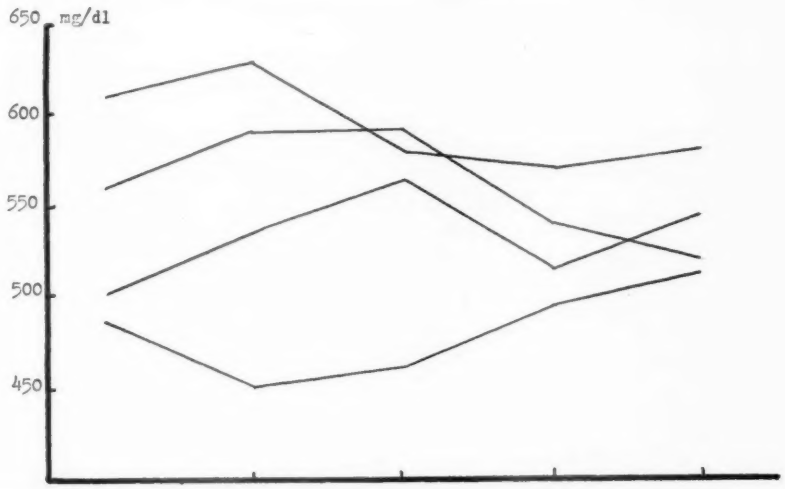
The clinical findings were similar to our experiences with dogs. Fig. 3 shows the anastomosed portion of the pancreatic duct and jejunal mucosa in a

*Experiment performed by Dr. Fujimoto.

A. *B.*

Fig. 4.—The excretion of injected radiopaque substance from pancreatic duct after mucosa-to-mucosa anastomoses. *A*, Before excretion. *B*, After excretion.

TABLE II. THE RESULTS OF PROSTIGMIN TEST FOLLOWING RADICAL PANCREATODUODENECTOMY WITH MUCOSA-TO-MUCOSA PANCREATOJEJUNOSTOMY



CASE	BEFORE INJECTION	AFTER INJECTION			
		30 MIN.	60 MIN.	90 MIN.	120 MIN.
S. M.	501	532	565	515	544
T. T.	488	452	467	490	513
E. M.	554	589	592	542	531
K. S.	611	627	583	571	580

patient with carcinoma of the pancreatic head who died from recurrence 10 months after radical pancreaticoduodenectomy. At autopsy, the anastomosis was found to be widely patent.

This patient was studied after surgery by means of a radiopaque substance introduced into the pancreatic duct through plastic tubing which had been placed there at surgery. After removing the tube, the material was found to be excreted within 10 minutes. Fig. 4 shows that the anastomosis was widely patent.

The prostigmin test[12] postoperatively revealed that the anastomosis was patent (Table II).

From these clinical and experimental studies, it appears that the mucosa-to-mucosa type of anastomosis is superior. The anastomosis must be performed over a plastic tube splint, using one or two interrupted silk sutures. Porth,[6] Reynolds,[7] Silver,[8] Varco,[10] and Yoshioka[14] have used short tubes fixed at the anastomosis. In our patients, a long vinyl tube was inserted into the pancreatic duct and brought out via the jejunum, stomach, and nose. The tube is fixed at the pancreaticojejunal and gastrojejunal anastomoses and the nose. The pancreatic secretions were aspirated for 10 days following surgery. Since jejunal peristalsis sometimes causes the tube to be dislodged, fixation is necessary. The use of long vinyl tubes has the following merits: (1) If a short splint is passed into the jejunum soon after surgery, suture line breakdown and obstruction may result; the use of a long vinyl tube prevents this. (2) Continuous aspiration of the pancreatic juice postoperatively should benefit anastomotic healing and prevent the formation of fistulas. If there is no drainage, the tube has slipped out of the duct, is angulated, or obstructed. This can be verified by the injection of a radiopaque material and suitable measures taken. The excretion of pancreatic juice through such a tube postoperatively is shown in Fig. 5. (3) The long vinyl tube effectively splints the pancreaticojejunal anastomosis until this area is completely covered by mucosa. (4) The long tube splint can be removed with ease whereas the fate of a short tube left in place is uncertain.

CHOLEDOCHOJEJUNAL ANASTOMOSIS

To prevent stricturing at the choledochojejunal anastomotic site, a long vinyl tube is also used as a splint. This is brought out through the jejunum, stomach, and nose and is allowed to remain in place for a week postoperatively. Continuous aspiration of bile is carried out.

NEW METHOD OF PANCREATICODUODENECTOMY

Our second method of pancreaticoduodenectomy splinting the points of anastomosis (Fig. 6) was used with good results in a number of cases. Anastomotic breakdown or stricturing was not found in any of these. Child,[1] Dennis,[2] Hunt,[4] Pearse,[5] and Whipple[11] have reported that one must maintain a distance of 30 cm. or more between the choledochojejunostomy and gastrojejunostomy to prevent ascending cholangitis. From our experience this seems to be necessary. When the patients are observed over a long period of time (the longest is 4 years on our services), however, digestion and absorption of

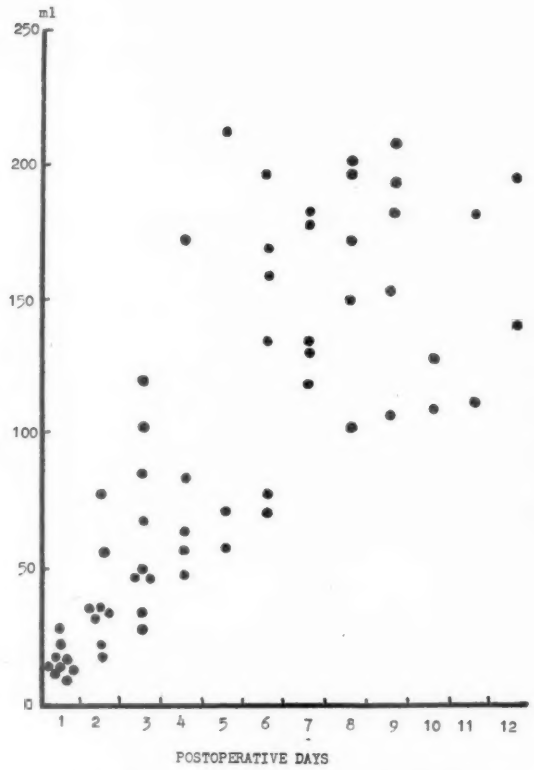


Fig. 5.—The excretion of pancreatic juice after mucosa-to-mucosa pancreatojejunostomy.

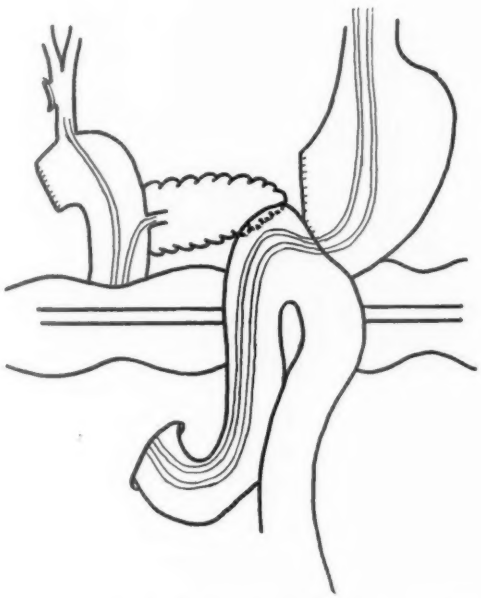


Fig. 6.—Our second method of pancreaticoduodenectomy employing long vinyl tube.

protein and fat gradually diminishes after surgery (Table III). Parallel to this, liver function diminishes and is shown by the Takata reaction,[9] thymol turbidity test, and Millon's value[13] (Table IV). The progressive decline in the pancreatic and liver function is probably the result of persistent reflux of food into the duct system and ascending infection. Figs. 7, 8, and 9, show that opaque media enter the biliary tree with this type of anastomosis.

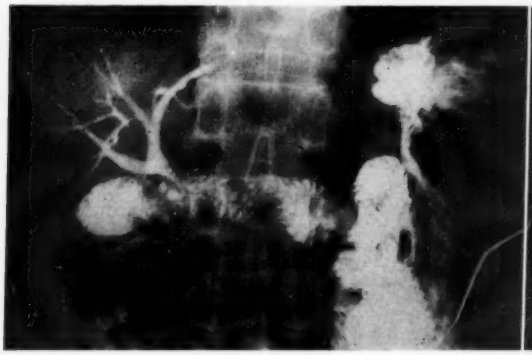


Fig. 7.

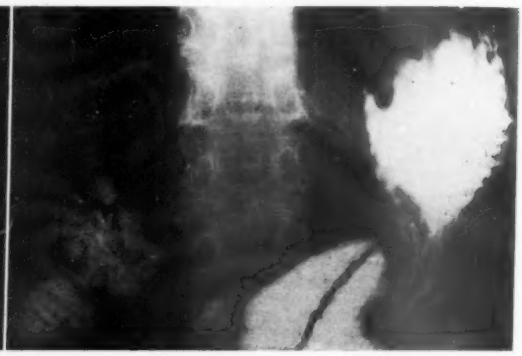


Fig. 8.

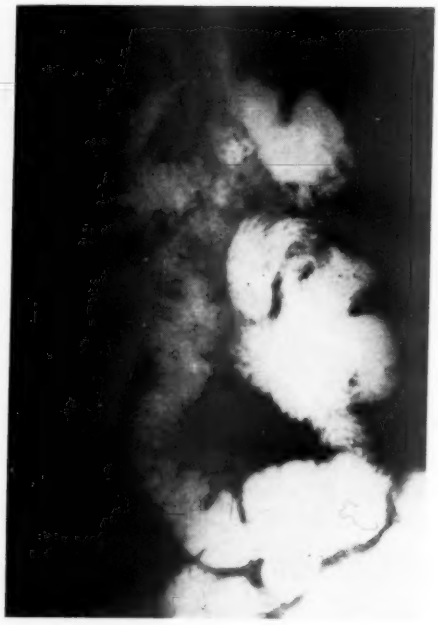


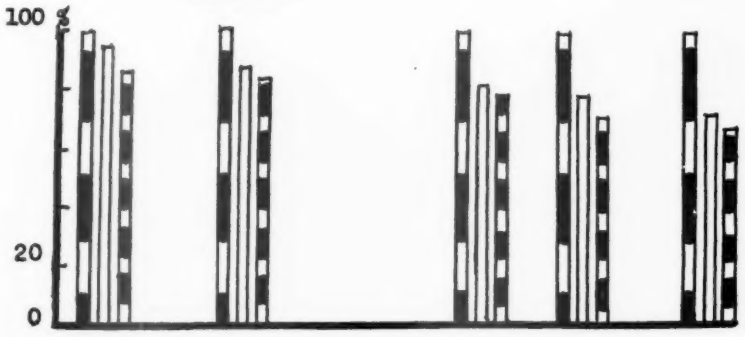
Fig. 9.

Figs. 7, 8, and 9.—The reflux of barium sulfate into biliary tree after our second method of pancreaticoduodenectomy. 7, A 57-year-old man. 8, A 51-year-old man. 9, A 60-year-old woman.

In an attempt to obviate this complication, an end-to-end anastomosis between stomach and jejunum, our first method, was employed (Fig. 10). The gastrojejunal, choledochojejunal, and pancreaticojejunal anastomoses were made to simulate the normal anatomy. This method has been carried out in 5 patients in whom postoperative x-ray studies revealed no reflux of barium into

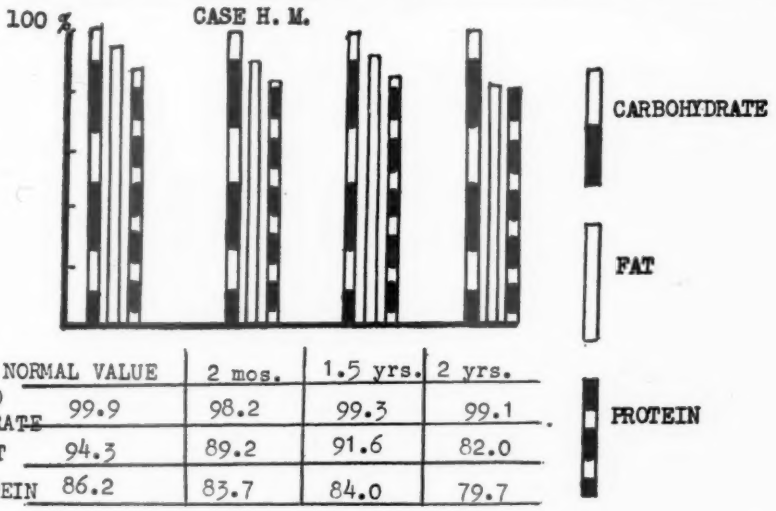
TABLE III. POSTOPERATIVE ABSORPTION RATIO OF CARBOHYDRATE, FAT, AND PROTEIN AFTER OUR SECOND METHOD OF PANCREATICODUODENECTOMY

CASE M. K.



	NORMAL VALUE	2 mos.		2 yrs.	2.5 yrs.	3 yrs.
CARBO HYDRATE	99.9	99.6		99.2	99.8	99.0
FAT	94.3	87.7		82.5	78.5	71.9
PROTEIN	86.2	83.3		77.2	71.4	65.5

CASE H. M.



	NORMAL VALUE	2 mos.	1.5 yrs.	2 yrs.
CARBO HYDRATE	99.9	98.2	99.3	99.1
FAT	94.3	89.2	91.6	82.0
PROTEIN	86.2	83.7	84.0	79.7

the biliary system. This is an interesting finding which might be explained by the lack of stasis in the area of the choledochojejunal anastomosis. The pressure relationship between the common duct and jejunum probably prevents reflux. However, with our second method of pancreaticoduodenectomy we have been able to demonstrate that reflux occurs into the proximal jejunal loop. Antiperistalsis has been thought to be responsible for this phenomenon.

X-ray examination in the cases in which the end-to-end anastomosis was performed revealed that food did not enter the bile or pancreatic ducts (Figs. 11 and 12). Therefore, after this type of procedure, ascending infection with consequent liver failure probably does not occur. To maintain good liver and pancreatic function following radical pancreaticoduodenectomy, our first method of using this type of anastomosis appears to be a solution of the problem of reflux.

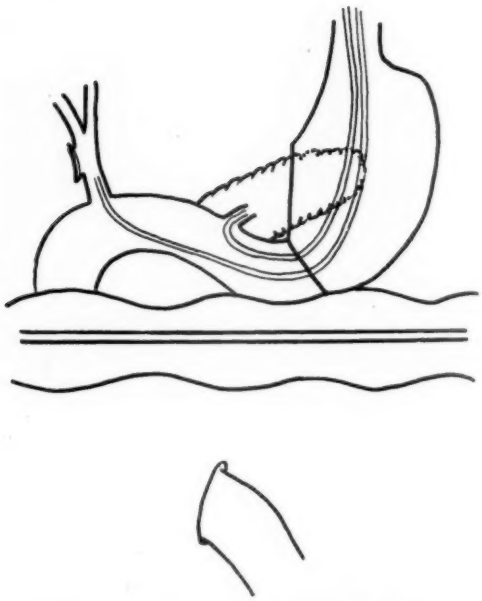


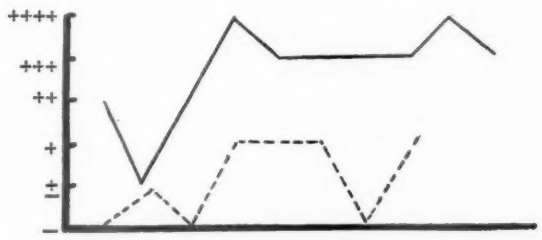
Fig. 10.—Our first method of pancreaticoduodenectomy employing long vinyl tube.

Fig. 11. Fig. 12.

Figs. 11 and 12.—X-rays showing absence of reflux into the biliary tree of oral barium sulfate following our first method. *11*, A 49-year-old man. *12*, A 6-year-old girl.

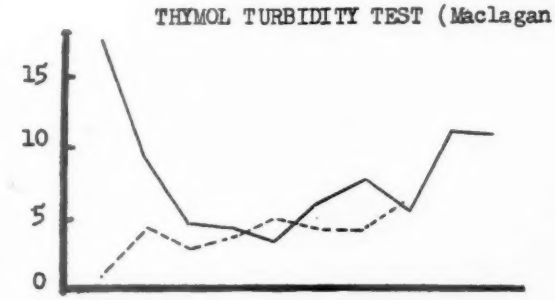
TABLE IV. POSTOPERATIVE LIVER FUNCTION TESTS AFTER OUR SECOND METHOD OF PANCREATICODUODENECTOMY

SERUM TAKATA REACTION

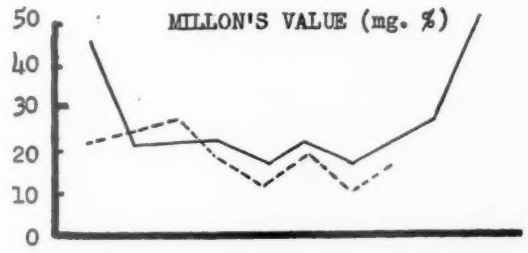


CASE	BEFORE SURG.	2 MO.	0.5 YR.	1 YR.	1.5 YR.	2 YR.	2.5 YR.	3 YR.	3.5 YR.	4 YR.
M. K.	++	±	++	++++	+++	+++	+++	+++	++++	+++
H. M.	−	±	−	+	+	+	−	+		

THYMOL TURBIDITY TEST (Maclagan unit)



CASE	BEFORE SURG.	2 MO.	0.5 YR.	1 YR.	1.5 YR.	2 YR.	2.5 YR.	3 YR.	3.5 YR.	4 YR.
M. K.	17.5	9.0	4.6	4.4	3.4	6.1	7.6	5.5	11.0	10.6
H. M.	1.1	4.4	2.8	3.6	5.0	4.1	4.1	5.8		



CASE	BEFORE SURG.	2 MO.	0.5 YR.	1 YR.	1.5 YR.	2 YR.	2.5 YR.	3 YR.	3.5 YR.	4 YR.
M. K.	45.2	20.5	22.0	24.0	17.5	22.5	17.5	22.0	27.5	50.5
H. M.	22.0		27.0	17.0	12.0	19.0	9.0	15.0		

SUMMARY AND CONCLUSIONS

1. In pancreaticoduodenectomy, there is evidence in both dogs and humans that mucosa-to-mucosa anastomosis at the site of pancreaticojejunostomy is superior to the mere implantation of the pancreatic stump.

2. The pancreaticojejunostomy and choledochojejunostomy are splinted and allowed to drain postoperatively via long vinyl tubes which are brought out through the nose.

3. An end-to-end anastomosis between the stomach and jejunum is shown to overcome the problem of reflux into the biliary tree.

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EXPERIMENTAL HEMORRHAGIC PANCREATITIS PRODUCED BY STAPHYLOCOCCAL TOXIN

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THE injection of a dilute staphylococcal toxin into the large pancreatic duct of dogs following permanent ligation of both ducts results in a necrotizing hemorrhagic pancreatitis.[17] Thal's description of this technique demonstrated that the pancreatic necrosis and hemorrhage were a result of the effects of the toxin upon the small blood vessels within the parenchyma of the pancreas. The vascular lesions produced by this experimental condition are similar to those seen in fatal hemorrhagic pancreatitis in human beings.

In the present work, acute hemorrhagic pancreatitis was produced in dogs by the intraductal injection of staphylococcal toxin. Thal's technique was modified by eliminating the permanent ligation of the pancreatic ducts. Preliminary studies on the effects of penicillin and hydrocortisone are presented.

MATERIALS AND METHODS

1. Mongrel dogs, weighing from 5 to 18 Kg., were used. They were kept under observation for a minimum of 2 weeks prior to operation.

2. Operations were performed with the animal under Nembutal anesthesia and through a right rectus upper abdominal incision.

3. The staphylococcal toxin was from the Wood 46 strain.* Saline dilutions of the toxin were injected into the pancreatic duct by means of a Luer-Lok syringe and fine gauge needle.

4. Serum amylase determinations were made using the method of Somogyi. The normal range in dogs in this laboratory is up to 3,000 units.

5. Food and water were withheld from all animals for 24 hours following operation. Dogs were autopsied as soon after death as possible and microscopic sections made of the pancreas and other organs. Survivors were sacrificed and autopsied 2 to 4 weeks following operation so that changes in the pancreas and other organs at this stage in the experiment could be evaluated.

EXPERIMENTS AND RESULTS

Series 1 (10 Dogs).—The large (accessory) pancreatic duct was isolated and temporarily occluded by ligature at its entrance into the duodenum. No attempt was made to identify the smaller duct (Wirsung's duct). Through

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*Supplied by Lederle Laboratories.

a 25 or 27 gauge needle, 0.5 c.c. per kilogram of a 1:5 dilution of staphylococcal toxin was injected into the pancreatic duct. Three minutes after injection of the toxin, the ligature was removed. Care was taken to minimize the trauma to the duct.

The inconsistent results (Table I) were attributed to the failure to occlude the smaller pancreatic duct during the injection of the toxin. A large communication between the main and accessory ducts may occur within the pancreas of the dog (Fig. 1), and others have also emphasized the importance of occluding both ducts simultaneously to prevent the injected material from refluxing into the duodenum during the injection.[1]

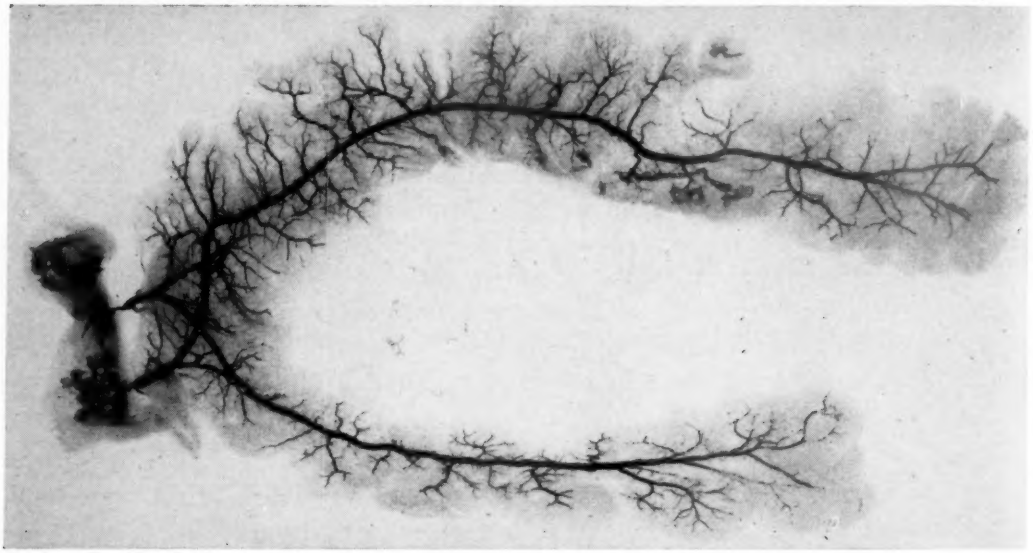


Fig. 1.—Photograph showing dog pancreas with ductal system outlined. Note large communication between main and accessory duct.

TABLE I. EFFECT OF OCCLUDING PANCREATIC DUCTS DURING INJECTION OF 1:5 DILUTION OF STAPHYLOCOCCAL TOXIN

	NUMBER OF DOGS	SURVIVAL TIME	AUTOPSY FINDINGS
Series 1. (Large duct occluded)	3	17, 23, and 28 hours	Acute hemorrhagic pancreatitis
	1	40 hours	Acute hemorrhagic pancreatitis and colon perforation
	3	7, 7, and 12 days	Bile peritonitis due to gall bladder perforation
	3*	13, 22, and 27 days	Pancreatic fibrosis
Series 2. (Both ducts occluded)	10	10 to 17.5 hours (average 14.3)	Acute hemorrhagic pancreatitis

*Sacrificed.

Three dogs in this series died in 7 to 12 days of bile peritonitis due to perforation of the gall bladder. Common bile duct obstruction due to pancreatitis may have contributed significantly to this finding.

Series 2 (10 Dogs).—Both pancreatic ducts were occluded by ligature at their entrance into the duodenum. A 1:5 dilution of staphylococcal toxin

(0.6 c.c. per kilogram) was injected into the larger duct. Three minutes following the injection, both ligatures were removed.

For reasons explained in the preceding section, Series 1, both pancreatic ducts were temporarily occluded in this manner in all subsequent experiments. If the smaller pancreatic duct could not be identified, the dog was excluded from the experiment. This second duct was not found in 5 per cent of the animals.

A uniformly fatal hemorrhagic pancreatitis was produced without permanent obstruction of the pancreatic ducts (Table I). There was extensive hemorrhage and necrosis throughout the pancreas, with approximately 300 c.c. of dark, hemorrhagic fluid in the peritoneal cavity. Large areas of fat necrosis were present in the peripancreatic region and in the greater omentum. A hemorrhagic duodenitis was present in each dog.

Series 3 (10 Dogs).—Pancreatitis was produced in 3 dogs by using a 1:7.5 dilution of toxin, in 5 dogs by using a 1:8.5 dilution, and in 2 dogs by using a 1:10 dilution. These dilutions were used in order to produce a less fulminating pancreatitis than found in Series 2.

Although the 1:7.5 and 1:8.5 dilutions of toxin caused death from acute hemorrhagic pancreatitis in the 8 animals, the pancreatic necrosis and hemorrhage was not as severe as that seen in Series 2. A 1:10 dilution of toxin did not produce a lethal form of pancreatitis.

Series 4.—Acute hemorrhagic pancreatitis was produced in 37 dogs by the intraductal injection of 0.6 c.c. per kilogram of a 1:9 dilution of staphylococcal toxin. The animals were divided into the following three groups and the results are outlined in Table II.

TABLE II. EFFECT OF PENICILLIN AND HYDROCORTISONE ON SURVIVAL IN PANCREATITIS PRODUCED BY A 1:9 DILUTION OF STAPHYLOCOCCAL TOXIN

GROUP	NUMBER OF DOGS	PER CENT	TIME OF DEATH
A. Untreated			
Survived	4	33	
Died	8	67	13 to 19.5 hr. (average 16.7)
B. Penicillin			
Survived	6	60	
Died	4	40	16.5 to 36 hr. (average 22.9)
C. Hydrocortisone			
Survived	11	73	
Died	4	27	15 to 29 hr. (average 20.3)

Group A: Twelve dogs received no treatment. Four of the 12 untreated animals (33.3 per cent) were considered survivors. Throughout these studies, death solely due to acute hemorrhagic pancreatitis occurred within 36 hours after injection of the toxin. In Series 2, 3, and 4, the 7 dogs that died later than 36 hours (5 to 14 days), died from severe infection in the pancreas, lung, or other organs.

Group B: Ten dogs received 800,000 units of penicillin* intramuscularly every 12 hours for 3 days beginning at operation.

The 60 per cent survival rate in the penicillin-treated group does not represent a statistically significant increase in survival over the untreated group. However, in contrast to survivors in the untreated and hydrocortisone-treated groups, those treated with penicillin had no evidence of infection in the pancreas or other organ at the time of sacrifice.

Group C: Twelve dogs received 25 mg. per kilogram of hydrocortisone† intramuscularly at operation and again at 24 and 48 hours if they were still alive. Three dogs received 25 mg. per kilogram hydrocortisone† intramuscularly at operation and every 6 hours for 24 hours, then 12.5 mg. per kilogram every 12 hours for 24 hours.

Seventy-three per cent of the hydrocortisone-treated dogs survived the acute phase of the experiment. The improved survival over the untreated group was statistically significant at the 0.05 level of confidence as measured by the T-test, and at the 0.1 level by the Chi^2 method.

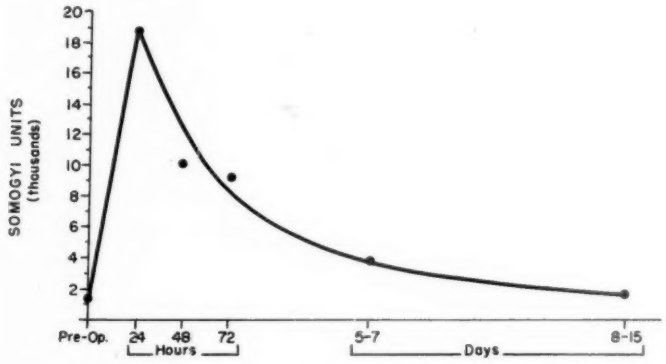


Fig. 2.—Composite graph of serum amylase levels in dogs with pancreatitis produced by 1:9 dilution of staphylococcal toxin. No differences were noted among untreated, penicillin-treated, and hydrocortisone-treated animals.

Laboratory data in Series 4: Serum amylase values, shown from representative animals in Fig. 2, were essentially the same in the untreated, penicillin-treated, and hydrocortisone-treated dogs.

Only 3 of the 37 dogs failed to show a rise in hematocrit during the first 24 hours. These 3 received hydrocortisone every 6 hours and showed a drop in hematocrit of approximately 4 per cent instead of the 5 to 10 per cent rise due to hemoconcentration seen in the other animals.

All dogs had a significant rise in total white blood cells within 24 hours following operation. The count remained high throughout the experiment in the untreated and steroid-treated animals but returned to normal in those dogs treated with penicillin.

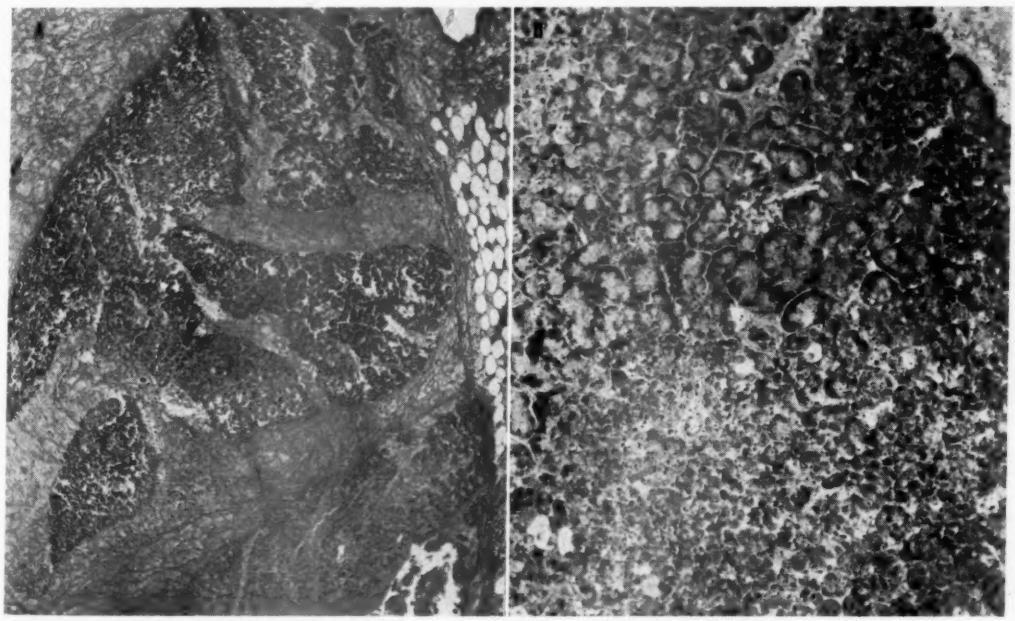
No distinct difference in gross or microscopic appearance of the pancreas was seen among nonsurvivors in Series 4. The photomicrographs in Fig. 3

*Ledercillin supplied by Lederle Laboratories.
†Cortef supplied by The Upjohn Company.

illustrate the fatal pancreatitis produced by the 1:9 dilution of the staphylococcal toxin.

DISCUSSION

Abnormalities in pancreatic blood flow may be an important factor in the etiology of acute hemorrhagic pancreatitis in man. The use of the staphylococcal toxin, as described by Thal and modified in these experiments, constitutes a desirable method for the study of experimental pancreatitis as a disease of vascular etiology. The necrosis and hemorrhage produced by the toxin closely resemble that found in human pancreatitis, and result from the progressive engorgement, thrombosis, and rupture of the small vessels located within the parenchyma of the pancreas.[17] Although similar lesions are produced experimentally with alteration of the major pancreatic blood supply,[3, 8-10] and with certain sensitivity phenomena,[11, 15, 16] such methods are complex and require complete ductal obstruction, which is rarely seen in human cases of pancreatitis. The technique using the staphylococcal toxin permits aseptic conditions, does not involve complicated operative procedures, and avoids permanent obstruction of the pancreatic ducts.



A. *B.*

Fig. 3.—Photomicrographs demonstrating pancreatitis in dogs produced by a 1:9 dilution of staphylococcal toxin (*A* ×35, *B* ×120; reduced 5/11).

These studies and other experimental[2, 14] and clinical[4, 6, 7, 12, 13] reports indicate that the adrenocortical hormones increase survival in acute hemorrhagic pancreatitis. Although the mode of action of these drugs in this disease has not been determined, the recent identification of isoantibodies in the serum of patients and experimental animals with pancreatitis,[18] suggests that the steroids may inhibit certain sensitivity phenomena which are capable of

producing vascular lesions in the pancreas. The theoretical consideration of sensitivity in human pancreatitis must include (1) possible sensitization of the pancreas to foreign materials which may initiate the vascular damage, and (2) sensitization to substances produced by inflammation and necrosis in the pancreas itself. The beneficial effects of the steroids in experimental pancreatitis may be due to interference with the latter autoimmune reaction.

The successful use of hydrocortisone in combating surgical shock in human beings and laboratory animals offers another possible explanation for the effectiveness of this drug in the treatment of acute hemorrhagic pancreatitis. The mechanism by which hydrocortisone and related compounds elevate the blood pressure and prevent irreversible shock is unknown, but may involve the influence of the steroids on the animal's vascular response to norepinephrine.[5]

The clinical use of cortisone and hydrocortisone in acute pancreatitis is generally limited to severe cases which do not respond to treatment with blood, intravenous fluids, nasogastric suction, anticholinergic drugs, sedation, and antibiotics. The routine administration of adrenocortical steroids during the early stages of acute pancreatitis may reduce the morbidity and mortality of this disease in man.

SUMMARY

1. The injection of a dilute staphylococcal toxin into the pancreatic duct of the dog, without permanent ductal obstruction, results in acute, necrotizing, hemorrhagic pancreatitis. Variation of the concentration of toxin injected alters the severity of the pancreatitis.

2. Preliminary studies on the effect of penicillin and hydrocortisone in this experimental form of pancreatitis show that penicillin is of no apparent value in the acute phase, but reduces the incidence of later complications due to infection. Hydrocortisone increases survival in the acute phase.

3. The beneficial effects of the adrenocortical hormones in acute hemorrhagic pancreatitis may result from the ability of these steroids to inhibit sensitivity phenomena which cause vascular lesions in the pancreas.

We wish to thank Dr. Pedro C. Jaena for assisting in the experiments, and Dr. Rowena Spencer for preparing the dog pancreas shown in Fig. 1.

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MEAN CORPUSCULAR VOLUME OF ERYTHROCYTES AND HEMATOCRIT IN EXPERIMENTAL BURNS

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THE hematocrit represents the volume of erythrocytes in relation to total blood volume. A rise in hematocrit can be the result either of losses of blood plasma in excess of red blood corpuscles or of an increase in cell volume in excess of blood plasma.

Determinations of the hematocrit are often used in clinical practice as a quick method for the evaluation of intravascular fluid loss. Thus it is generally assumed that a rise of hematocrit in burns is caused mainly by a loss of blood plasma without a corresponding loss of red cells.

No systematic investigation has been carried out to date concerning the possible increase of red cell volume in burns. This factor merits attention since certain morphologic changes are known to occur in erythrocytes under thermal influence. Fragmentation of red cells in vitro due to heat has been described as early as 1865[12] and takes place at temperatures of 51° to 65° C. It is assumed to be an effect of the direct action of heat on erythrocytes.[13] Furthermore, the appearance of microspherocytes and fragmented forms in blood smears made promptly after burns in humans has been reported.[13] Alterations in mean corpuscular volume (M.C.V.) were so variable, however, as to provide no conclusive evidence of definite changes in cell size due to burns.[2]

Swelling of erythrocytes was observed in vitro within the temperature range of 55° to 61° C. A comparison of hematocrit and hemoglobin content in pigs exposed to 75° C. lead to the assumption that most of the early increase in cell volume was a product of the swelling of erythrocytes rather than loss of plasma or mobilization of cells from storage depots. The M.C.V. was, however, not determined.[7]

These studies suggest that the hematocrit in burns may be considerably affected by changes in erythrocyte volume in addition to those in plasma volume. This might be of importance in view of the treatment of burned patients.

The aim of this paper was to examine systematically the significance of changes in erythrocyte volume for the hematocrit in burns. For this purpose

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rats were subjected to standard experimental burns and the M.C.V. as well as the spherical index (i) determined by measuring hematocrit, number, and mean corpuscular diameter (M.C.D.) of red blood corpuscles.

METHODS

Male albino rats weighing on the average 280 Gm. (195 to 420 Gm.) were anesthetized with an ether-oxygen mixture. Immersion of the shaved backs in water at 90° C. for 30 seconds produced third-degree burns involving an average of 32 per cent (25 to 50 per cent) of the body surface. Immediately following thermal exposure the rats were dried thoroughly and placed into special wire-mesh cages which, while keeping the animals nearly motionless, allowed the tails to protrude.

Hematocrit and cell count were determined and blood smears made at various intervals after the thermal injury from blood withdrawn from the tail or—in rare cases—from the heart of anesthetized rats. Heart blood heated in vitro was exposed to various temperatures for 1 minute's duration, placed in a water bath at 36° C., and examined upon the elapse of one-half hour. Rats treated identically with the exception of the thermal injury served as controls.

Each hematocrit was averaged from 4 pipettes contrifuged simultaneously at 1,300 g for 15 minutes. A minute pink, transparent layer interposed between the packed red corpuscles and the buffy coat was sometimes encountered, almost without exception, in blood from burned animals. Since its composition is uncertain it was disregarded.

Erythrocyte counts were made with at least two separate pipettes in each case. The blood, diluted 1:200, was shaken for 6 to 8 minutes (high cell counts!). Approximately 2,000 corpuscles were counted for each sample. To this end only erythrocytes with a diameter no smaller than one-half of the norm were considered. Smaller particles, averaging 1.8 per cent (0.4 to 4.2 per cent) of the former in number, were listed separately.

Blood smears, air-dried and stained panoptically by the method of Pappenheim, were used to determine the M.C.D. Each Price-Jones curve was constructed from not less than 200 cells from at least two blood smears. Postburn curves showed a slight unilateral distortion in the region of the lowest values; for the calculation of the M.C.D., standard deviation (σ), and coefficient of variation, only that portion of a curve which most closely resembled a normal distribution was selected.

The mean corpuscular volume (M.C.V.) in millimicron^3 was calculated from the equation: $\text{M.C.V.} = \frac{\text{H} \times 10}{\text{E.C.}}$ where E.C. represents the erythrocytes count per millimeter^3 in millions and H the hematocrit. The spherical index (i) was computed from the formula: $\text{i} = \frac{4\ \text{V}}{\text{pi}\ \text{d}^3}$ where d represents the diameter. A perfect sphere would have an i equal to 0.667. Calculations of the significance of the statistical data were made with the aid of Gosset's t tests.[4]

SOURCES OF ERROR

Hematocrit.—The error due to variations in the speed of centrifugation was low. Deliberate raising of the speed from 2,500 to 3,500 r.p.m. lowered the hematocrit from 45.5 to 44.4 per cent in one case—corresponding to a coefficient of variation of 2.4 per cent—while at 4,000 r.p.m. the hematocrit was unchanged as compared to 3,500 r.p.m. Spontaneous variations in the rate of spin never exceeded 300 r.p.m.

Erythrocyte Count.—This introduces the principal source of error of all the measurements. The coefficient of variation of parallel samples was about 3 per cent. In rare cases, where duplicate determinations diverged excessively, additional counts generally permitted the rejection of one aberrant value.[8] Changes in M.C.V. observed (Figs. 1 and 3) were of a greater order of magnitude (cf. Results). Successive control counts from the same pipette seldom differed appreciably so that the trauma inflicted by shaking, even when repeated, was probably minimal.

Blood Smears.—The degree of precision reached for the M.C.D. determinations was satisfactory, judging from successive samples taken from a control rat, as is shown in Table I. Values for the M.C.D. thus obtained have only relative validity for, contrary to older claims,[15] erythrocytes shrink while drying to the extent of 0.5 to 1.0 mμ. Nevertheless, wet cells which are not flat discs may actually increase in diameter through spreading when dried in films.[11]

TABLE I

HOUR	M.C.D. (mμ)	SIGMA ($\pm$ mμ)	COEFFICIENT OF VARIATION (%)	RANGE (mμ)
0	6.1	0.47	7.7	4.2-7.5
1¼	6.1	0.42	6.9	4.8-7.5
4¼	6.0	0.40	6.7	4.8-7.2

Effect of Microspherocytes and Fragments.—If these deliberately disregarded particles resulted from the splitting up of erythrocytes, the number of red cells would probably be reduced thereby. This would simulate an increased M.C.V. Neglected small particles which according to our determinations amounted to 1.8 per cent and measured less than 3 mμ in diameter correspond to less than 0.5 per cent of the total erythrocytes. This induces a negligible error of less than 0.5 per cent in the cell count and hence in calculations of the M.C.V.

Packing Error and Hemolysis.—An increase in volume or in spherical index as well as the appearance of irregular red cells might cause a "packing error" in the hematocrit readings and lead to artificially high M.C.V. calculations. Erythrocytes, however, are elastic bodies and can be expected to adapt themselves plastically to one another during centrifugation. Indeed an analysis of blood heated in vitro showed that at the higher temperatures spherocytes were obtained whose volume, as determined by direct microscopic measurement, was if anything greater than computed from the hematocrit and cell count. What holds true for these extreme conditions is even more likely to apply to those prevailing in vivo. Furthermore it is conceivable that relatively more erythrocytes hemolyzed during centrifugation than during the shaking of the counting

pipettes. At high speeds of centrifugation a certain loss of intracellular fluid through expression might also be a possible factor. A spreading effect in the blood smear could artificially enlarge the M.C.D. Through all these mechanisms the M.C.V. and spherical index, respectively, would be depressed below their true values.

RESULTS

The average M.C.V. as calculated from all the individual values between 1 and 6 hours after the thermal injury was 5.8 per cent higher in burned than in control animals. This difference was significant ($P < 0.001$) (Fig. 1).

The curve representing the average M.C.V. of the burned rats was in all points elevated over that of the controls. However, only the point corresponding to the second hour differed significantly from the control value ($0.02 < P < 0.05$). This difference, amounting to 10.3 per cent was the largest reached over the observation period.

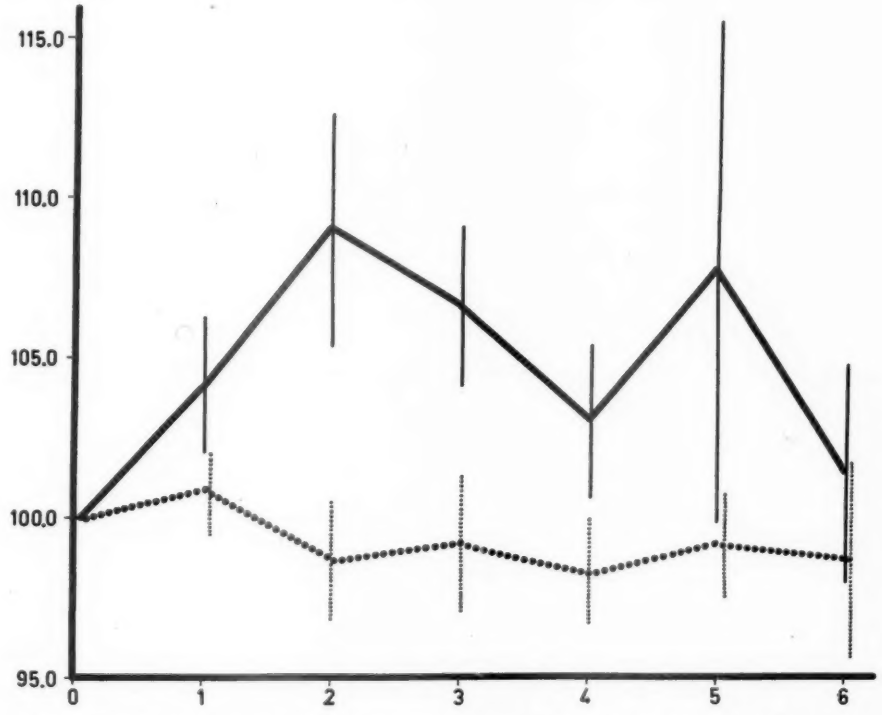

Fig. 1.—Behavior of the M.C.V. of 20 burned rats and 12 control rats. ——— Burned rats. - - - - - Control rats. Ordinate: M.C.V. in per cent (control value = 100 per cent). Abscissa: hours after thermal injury. Vertical lines: standard deviation of the mean values.

The average mean hematocrit reading, computed from all the individual values between 1 and 6 hours postburn, exceeded that of the control rats by 31.5 per cent. This difference likewise was significant ($P < 0.001$) (Fig. 2). The progressive decline in hematocrit in the control animals is probably due to the blood withdrawals.

The percentage increase in mean corpuscular volume during the first 3 hours in 9 rats accounted for 20 to 100 per cent (average 67 per cent) of the simultaneous rise in hematocrit (Fig. 3). In the rest of the animals the percentage was lower than 20 per cent.

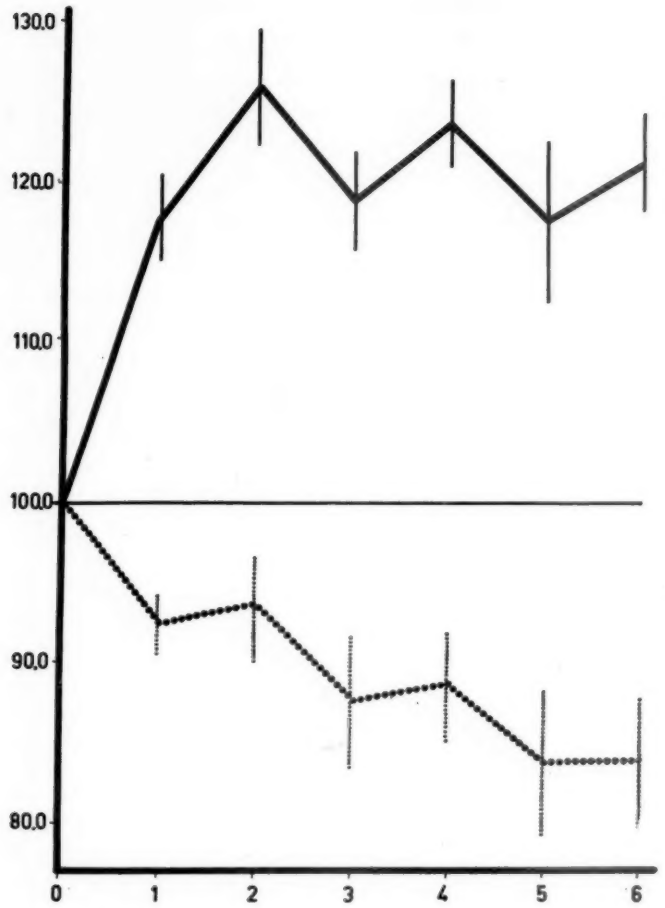

Fig. 2.—Behavior of the hematocrit of 20 burned rats and 12 control rats. ——— Burned rats. - - - - - Control rats. Ordinate: hematocrit in per cent (control value = 100 per cent). Abscissa: hours after thermal injury. Vertical lines: standard deviation of the mean values.

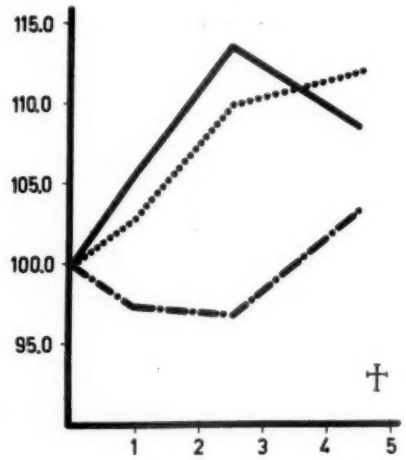

Fig. 3.—Behavior of the M.C.V., hematocrit, and erythrocyte count in a burned rat (No. 21) in per cent (control values = 100 per cent) (ordinate). Abscissa: hours after thermal injury. ——— M.C.V. •••• Hematocrit. - - - - - Erythrocyte count.

The spherical index of the erythrocytes of 5 burned rats showed an average increase of 16 per cent (+4 to +23 per cent) within the first 2½ hours after the burn (Table II).

TABLE II. CHANGES IN SPHERICAL INDEX OF ERYTHROCYTES IN RATS EXPOSED TO 90° C. FOR 30 SECONDS

RAT NUMBER	TIME AFTER THERMAL INJURY (HOURS)	MEAN CORPUSCULAR DIAMETER ($m\mu \pm \sigma$)	MEAN CORPUSCULAR VOLUME ($m\mu^3$)	SPHERICAL INDEX		MICROSPHEROCYTES AND FRAGMENTS (PER CENT OF REGULAR FORMS*)
				ABSOLUTE	PER CENT INCREASE (CONTROL = 100)	
4	control	6.1 ± 0.47	53.0	0.30		0.0
	2½	6.1 ± 0.51	58.9	0.33	110	7.3
5	control	6.5 ± 0.54	49.4	0.22		0.0
	1	6.6 ± 0.54	61.5	0.27	123	5.6
8	control	6.4 ± 0.43	50.6	0.24		0.0
	2½	6.3 ± 0.42	57.3	0.30	125	7.3
21	control	6.2 ± 0.46	51.1	0.28		0.0
	1	6.2 ± 0.47	54.0	0.29	104	2.5
	2½	6.2 ± 0.52	58.0	0.31	111	3.3
24	control	6.2 ± 0.39	47.7	0.26		0.0
	1	6.2 ± 0.45	57.7	0.32	123	1.8

*Not included in range or among values used to determine M.C.D.

Erythrocytes of 3 animals, whose blood was heated in vitro, showed increases in M.C.V. of 19 to 61 per cent over the starting values and a rise in spherical index up to 76 per cent (Table III). By microscopic observation the majority of the corpuscles had assumed spherical or nearly spherical shapes at the higher temperatures (56.0° to 66.5° C.).

TABLE III. CHANGES IN ERYTHROCYTES OF RAT BLOOD HEATED IN VITRO FOR 60 SECONDS

RAT NUMBER	TEMPERATURE (CENTIGRADE)	MEAN CORPUSCULAR DIAMETER ($m\mu \pm \sigma$)	MEAN CORPUSCULAR VOLUME		SPHERICAL INDEX		MICROSPHEROCYTES AND FRAGMENTS (PER CENT OF REGULAR FORMS*)
			$m\mu^3$	PER CENT INCREASE (CONTROL = 100)	ABSOLUTE	PER CENT INCREASE (CONTROL = 100)	
38	36.5 (control)	6.8 ± 0.45	54.6		0.22		0.7
	56.5	5.8 ± 0.65	75.8	138.7	0.50	227	3.9
39	36.0 (control)	6.7 ± 0.34	49.9		0.21		0.0
	47.5	6.5 ± 0.41	54.5	109.3	0.25	119	0.0
	56.0	6.5 ± 0.53	80.2	160.8	0.37	176	5.0
40	36.0 (control)	6.6 ± 0.36	66.1		0.30		0.0
	66.5	5.8 ± 0.49	78.6	118.9	0.50	167	8.8
	68.0	---------- hemolysis ----------					

*Not included in range or in values used to determine the M.C.D.

Microspherocytes and fragments arisen by detachment from heat-injured erythrocytes or representing the diminished remainders of these were regularly observed. Their number as estimated in the counting chamber averaged 1.8 per cent (0.4 to 4.2 per cent) of "normal" forms. In the Price-Jones curves they accounted for 4.8 per cent (0.5 to 8.8 per cent) and had a mean diameter of approximately 3.0 micra as compared to a normal modal class of 6.3 micra.

DISCUSSION

The rise in hematocrit in rats subjected to a standard experimental burn, as observed up to 6 hours following exposure, is probably due in part to an increase in the M.C.V. This appears evident from a comparison of Figs. 1 and 2. The increase in M.C.V. as calculated from the average of all the values from 1 to 6 hours is responsible for about 20 per cent of the average increase in hematocrit. The percentage rise in hematocrit due to an increase in M.C.V. exhibited, however, rather pronounced variations in individual cases. Thus it can account for a considerable fraction of the total rise in hematocrit. This is documented by 9 of the 20 burned rats which showed increases in M.C.V. exceeding 20 per cent of the increase in hematocrit within the first 3 hours. In 4 instances the entire increase was caused by a rise in M.C.V. (Fig. 3). Actually it is even possible that the percentage increase in M.C.V. be more marked than that of the hematocrit. This paradoxical behavior might be attributable among other factors to hemodilution. A further investigation of this problem is probably of interest.

It can be concluded that an early rise in hematocrit in experimentally burned rats is not an adequate criterion of fluid loss but may be largely the expression of an increased M.C.V. of the erythrocytes. This finding might be of importance for the evaluation of the hematocrit of burned patients and suggests that reliable information regarding fluid loss can be gained only by a determination of the M.C.V., that is, by a correlation of hematocrit and cell count.

Since the present investigation is concerned exclusively with the early changes in M.C.V. and hematocrit, further work will be necessary to determine later alterations.

The increase in M.C.V. in burned rats is probably produced by a rise in spherical index. The spherical index ($i = \frac{4\ V}{pi\ d^3}$)[9] is an expression of the relation between thickness and diameter of an erythrocyte. As the erythrocyte approaches its spherical critical volume, the spherical index becomes larger up to a maximum value of 0.667. An increase in spherical index is accompanied by an increase in M.C.V. provided the surface area remains constant because the quotient volume per surface is minimal for the biconcave disk and maximal for a sphere. In the course of the present experiments an increase in spherical index under thermal action has been found both in vivo and in vitro. This confirms earlier results in a limited number of patients[2] as well as in vitro observations.[13] It offers an explanation for the hemolysis following burns inasmuch as it is known that osmotic fragility increases with the spherical index.[9, 10]

While the swelling of erythrocytes heated in vitro was apparently a direct effect of temperature, additional factors are likely to affect the M.C.V. of erythrocytes in vivo. The finding, for example, that even the transfusion of large amounts of blood could not prevent the development of anemia in a severely burned patient speaks for other than temperature damage alone in the destruction of erythrocytes in vivo.[1] A relative hypotonicity of the plasma

through electrolyte and albumin displacements into the injured tissues,[1] the acidosis of shock,[3] and the influence of stasis[5, 7, 14] might result in an increase in M.C.V. Furthermore "toxins" from burned tissues have been reported to shorten the life expectancy of erythrocytes in vivo,[1] and it is possible that surface-active hemolytic substances causing an increase in M.C.V.[16] arise after burns.

The mechanism of the volume increase of the erythrocytes remains unknown. It seems possible that the osmotic pressure within the erythrocyte is greater than that in the plasma (protein content 5 times larger than in the plasma).[6] In order to compensate this intracellular osmotic pressure counteracting forces (for example, structural) would have to be present in the erythrocyte. Impairment of these would lead the osmotic forces to transform the biconcave disk progressively into a sphere, which has a larger volume than the disk. Structural damage of a more localized nature might explain the sprouting of bubbles and the fragmentation. Further studies will have to elucidate the role of these or other mechanisms in the increase of M.C.V. in thermal injuries.

SUMMARY

The role of changes in erythrocyte volume involved in the increase of hematocrit in experimental burns was investigated. For this purpose measurements of the mean corpuscular volume and spherical index were carried out 1 to 6 hours after thermal injury and compared with controls. Moreover determinations of the spherical index of erythrocytes heated in vitro were made.

The following results have been obtained:

1. In 20 burned rats the average mean corpuscular volume after thermal injury was 5.8 per cent and the average hematocrit was 31.5 per cent higher than in 12 controls. Both values were statistically significant ($P < 0.001$). Thus, 20 per cent of the average increase in hematocrit was produced by a rise in mean corpuscular volume.

2. In 9 of the 20 burned rats the rise in mean corpuscular volume accounted for more than 20 per cent and in 4 cases for 100 per cent of the rise in hematocrit within the first 3 hours postburn.

3. The spherical index was observed to increase both in vivo and in vitro, thus offering an explanation for the increase of mean corpuscular volume and for the hemolysis following burns.

From these experiments it can be concluded that the hematocrit is not an adequate criterion of intravascular fluid loss in the early stages of experimental burns. A possible increase of mean corpuscular volume of the erythrocytes has to be considered.

I wish to express my appreciation to P.D. Dr. K. Reber for his kind assistance.

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ORIGIN OF FIBROBLASTS FROM MONONUCLEAR BLOOD CELLS: A STUDY ON IN VITRO FORMATION OF THE COLLAGEN PRECURSOR, HYDROXYPROLINE, IN BUFFY COAT CULTURES

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IN 1904 Maximov reported that mononuclear white blood cells in sterile inflammatory exudates in rabbits undergo "transformation" into fibrocytes. Later (1928) he observed a similar transformation in culture using material from guinea pigs.

The hypothesis that such cells contribute to the fibrocyte population in the early stages of mammalian repair has received recent support from Gillmann (1955)[3] and Hartwell (1955).[5] Both worked with human cellular material, but were not agreed as to the type of white cells concerned. Allgöwer (1956)[1] and Hulliger (1957)[6] have reported the transformation of rabbit monocytes into fibrocytes in culture. The term "transformation" is used in this report without implying any comparison with the genetic term "bacterial transformation" (Hotchkiss).

It is clear from the literature, however, that the considerable body of work on this problem (for references, see Allgöwer[1]) has been based on morphologic identification. Transformed white cells have been described as fibrocytes on morphologic grounds only. Labeling cells in vivo with tritiated thymidine,[9] while giving a good indication of where DNA synthesis is going on, has to rely on morphologic criteria to ascribe this activity to certain cell types. It, therefore, does not constitute a fundamental departure from a morphologic approach to identify certain cell types and their precursors.

It appeared therefore of interest to determine whether blood cells, transformed into fibrocytes in culture, behave like fibrocytes in that they are synthesizing extracellular connective tissue elements. We have consequently tested the ability of rabbit blood buffy coat cultures to form hydroxyproline, an amino acid found in quantity only in connective tissue fibers.

We have found that over a culture period of 28 days, cultures forming fibrocytic networks are synthesizing hydroxyproline in quantities comparable to chick embryo connective tissue cultures.[6]

MATERIAL AND METHOD

Culture Method.—Adult male rabbits were used. Blood counts and smears were made from ear vein blood at 8 A.M., the animals having fasted overnight. About 40 ml. of blood was taken from each animal by cardiac puncture under

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aseptic conditions and transferred to siliconed 10 ml. centrifuge tubes. Syringe and tubes were cooled to prevent coagulation. No anticoagulants were used. The tubes with the blood were centrifuged immediately at 3,000 r.p.m. for 3 minutes, and the supernatant plasma was removed and refrigerated until it was needed. Plasma was stored in the frozen state and could usually be thawed and used in the liquid state for up to 4 days.

The tubes were then spun for a further period of 3 minutes at the same speed. The buffy coat was removed whole and cut into pieces of about 1 sq.mm. in area. Usually about 100 such pieces were obtained from one animal. Of these, 30 to 40 were selected by use of a table of random numbers, weighed together, and used for control of the hydroxyproline content of initial buffy coat. The remaining pieces were placed in groups of 8 into Carrel flasks for culture.

The initial culture medium consisted of 50 per cent autologous plasma and 50 per cent Gey's balanced salt solution containing 100 gamma ascorbic acid per milliliter. One and two tenths milliliters of this medium were placed into each Carrel flask. In 2 cases, however, the frozen plasma clotted when it was thawed and the addition made at 3 to 4 days was from a second animal. No differences in the course of culture were noted as a consequence of this variation in the treatment. Five to six days later, 0.5 ml. of 25 per cent rabbit serum in Gey's solution was added from a pool of rabbit serum. Repeated estimation of hydroxyproline in this serum gave negative results. The supernatant medium was changed at intervals of 5 to 6 days until the total culture period of 28 days had elapsed, the old serum being removed for the estimation of hydroxyproline before the addition of the new. At 28 days the supernatant serum was again removed and estimated—the plasma clot was removed whole from the Carrel flasks, and the fibrocytic colonies were identified microscopically and cut out with a knife. Obviously some of the plasma clot was included in this excision, since the cells had migrated into the clot. The remaining plasma was estimated separately. When transformed and nontransformed cultures were present in the same flask, the former were excised for separate estimation but the latter were not and were thus estimated with the remaining plasma. This was necessary since nontransformed cultures consisted only of a few round cells.

All material was weighed in sealed bottles before estimation. A number of cultures were fixed in Bouin's fluid for histologic examination by Gomori's silver method. Living cultures were photographed in Carrel flasks.

To test the method of cardiac puncture[1, 6] as to the possibility of picking up tissue fragments of the thoracic or cardiac wall, the following experiments were carried out:

a. Rabbits were bled to death by cardiac puncture, then 5 consecutive cardiac punctures were carried out as usual. The needle was washed with 0.2 ml. of Gey's solution, and the fluid was put into Carrel flasks and cultured as indicated above. Two animals were used for one experiment, 8 being the total of animals in this series.

b. A more crucial experiment as to possible contamination by cells of the integuments compared buffy coat cultures prepared from cannulated carotid

artery blood as opposed to buffy coat prepared by the usual cardiac puncture from the same animal. For technical reasons cannulation has to precede cardiac puncture in all the animals. Five animals were used for these experiments, one animal only being used at one time. Cannulation of the carotid artery was carried out aseptically using siliconed polyvinyl catheters. The first flush of blood was discarded. In 1 of the 5 animals, cardiac puncture was not successful. The results of the carotid buffy coat cultures of these animals are included, however, in the results.

Chemical Methods.—Hydroxyproline was estimated, using the method of Neuman and Logan.[10] Collagen was brought into solution by autoclaving it with distilled water at 2 atmospheres for 3 hours. Residues were autoclaved in 6N HCl for 4 hours at 2.5 at. to test whether or not all hydroxyproline had been removed in the first step. Color was developed by the method of Neuman and Logan and hydroxyproline content was determined by measuring absorption in a Zeiss spectrophotometer, using a blank containing all the solutions used in the samples, and comparing with distilled water standards containing known amounts of hydroxyproline. Maximum absorption was read at 5,600 Å and corrected for absorption at 6,400 and at 4,600 Å following Lothian[8] to exclude nonspecific absorption due to serum or tissue component.

The validity of this procedure was checked by recovery experiments in which known amounts of hydroxyproline were added to different sera. The mean per cent of recovery with serum pooled from 10 animals was 78 ± 5.5 per cent. It may be that hydroxyproline has been underestimated in our experiment.

In experiments 8 and 11, the plasma contained measurable amounts of hydroxyproline. The added plasma hydroxyproline was subtracted from the total hydroxyproline found in these experiments. The corrected results are shown in the last column of Table II.

RESULTS

In all 11 animals were used. From 7 of these cultures survived for the full period of 28 days. The mean white blood cell count of 11 animals before cardiac puncture was 8,290 ± 710. Table I gives the figures for the initial

TABLE I

ANIMAL	LEUKOCYTES PER MM.^{3}	TOTAL PIECES	HYDROXYPROLINE CONTENT: 0 DAYS		HYDROXYPROLINE PER 10 PIECES	PLASMA-HYDROXYPROLINE ADDED PER 10 PIECES
			NUMBER OF PIECES DETERMINED	MG. WEIGHT PER 10 PIECES		
1	6,540	80	35	20.6	0	0
2	10,140	135	40	16.1	0	5.5
3	7,700	144	40	24.5	0	0
4	7,000	131	40	19.0	0	0
5	11,790	159	40	22.5	0	0
6	—	119	35	22.3	0	0
7	7,660	83	35	20.2	0	0
8	6,610	139	35	21.1	0	3.6
9	9,600	109	35	18.8	0	0
10	7,530	120	40	18.7	0	0
11	6,280	109	40	22.3	0	4.8

material. The mean number of buffy coat pieces used for one experiment was 121 ± 8; of these 38 ± 1 were used for the initial hydroxyproline estimation. No hydroxyproline was detected in any of them. Their mean wet weight per 10 buffy coat pieces was 20.6 ± 0.7 mg.

For the 7 animals in which the cultures were carried successfully to 28 days the mean white cell count was 7,620 ± 750. From these 528 buffy coat cultures were made in all; 77 of these cultures (14.6 per cent) gave proliferation of fibrocyte-like cells.

When new medium was added during cultivation, the old medium (supernatant) was removed and hydroxyproline was estimated. Table II shows the amount of hydroxyproline found in medium removed from transformed and nontransformed cultures expressed in terms of 10 cultures. The mean total hydroxyproline content removed during 28 days from transformed cultures was 34.1 ± 7.2 gamma hydroxyproline and 1.9 ± 0.7 gamma from nontransformed cultures. These values are clearly significantly different.

TABLE II

EXPERIMENT	NUMBER OF CULTURES	HYDROXYPROLINE IN SUPERNATANT REMOVED DURING CULTIVATION FROM 10 CULTURES	HYDROXYPROLINE PER 10 CULTURES	PER CENT PLASMA CONTRIBUTION	TOTAL HYDROXYPROLINE PRODUCTION PER 10 CULTURES (IN CULTURES + SUPERNATANT − PLASMA CONTRIBUTION)
A. Hydroxyproline in transformed cultures and their media					
1	13	(8.5) incomplete	16.2	0	(24.7)
3	37	13.2	10.0	0	23.2
7	12	45.0	4.2	0	49.2
9	10	42.0	10.0	0	52.0
11	5	36.0	10.0	14	41.2
		34.1 ± 7.2	10.1 ± 1.9		41.4 ± 6.5
B. Hydroxyproline in nontransformed cultures and their media					
6	84	0.7	0.7	0	1.4
7	36	0.0	0.0	0	0.0
8	104	1.8	0.0	100	0.0
9	64	3.9	0.6	0	4.5
11	64	3.0	0.6	100	0.0
		1.9 ± 0.7			1.2 ± 0.9

At 28 days, cultures and plasma were removed from the flasks for estimation as described under "Methods." The mean wet weight per 10 transformed cultures with adherent plasma was 1,480 ± 344 mg. and their mean hydroxyproline content 10.1 ± 1.9 gamma (Table II). The hydroxyproline content of the remaining plasma and nontransformed cultures is also shown in Table II. Finally we have calculated the total hydroxyproline produced by transformed and nontransformed cultures by subtracting the hydroxyproline corresponding to a possible initial plasma contribution. The results are shown in the last column of Table II. Mean total hydroxyproline production for transformed cultures is 41.4 ± 6.5 gamma, for nontransformed cultures estimated together with their plasma mean total hydroxyproline production is 1.2 ± 0.9 gamma.

The experiments carried out to test for the possibility of cellular contamination gave the following results: Of 40 cardiac punctures in 8 different

animals 11 connective tissue cultures could be obtained which corresponds to one culture out of 4 cardiac punctures. Results of buffy coat cultures from cannulated carotid artery blood compared to buffy coat from cardiac puncture blood are listed in Table III.

TABLE III. RESULTS OF BUFFY COAT CULTURES FROM CANNULATED CAROTID ARTERY BLOOD COMPARED TO BUFFY COAT FROM CARDIAC PUNCTURE BLOOD (BOTH SAMPLES BEING TAKEN FROM THE SAME ANIMAL)

	NUMBER OF ANIMALS	NUMBER OF CARREL FLASKS	NUMBER OF CULTURES	TRANSFORMED CULTURES
"Heart" buffy coat	5	33	97	4 (4.6%)
"Carotid" buffy coat	5	100	343	30 (9%)

The percentage of connective tissue formation is two times higher in buffy coat cultures of cannulated carotid artery blood, than in blood aspirated from the heart.

Typical morphologic observations in carotid buffy coat cultures are given in Fig. 1 showing a small cell colony most probably arisen recently from one cell, and in Fig. 2 which gives part of a large connective tissue culture after 28 days in vitro.

DISCUSSION

Circulating blood cells have been found to transform and proliferate in vitro as fibrocytes. We have presented evidence that these fibrocytes form hydroxyproline in considerable amounts. Hydroxyproline is found in quantity only in extracellular connective tissue elements and its production in our blood cultures can be regarded as an index of the formation of such material. It constitutes some 13 per cent of collagen and is also present in collagen precursors.[4, 11] It is probable that its presence in the liquid medium indicates diffusion of some soluble precursor of reticulin.

It is probable that our values for total hydroxyproline production by transformed buffy coat cultures are underestimates, since the recovery of known amounts of hydroxyproline added to serum was only 78 per cent. We are unable to account for this finding, but it appears that serum in some way interferes with the development of the color reaction.

The fact that certain cellular elements of the circulating blood are in a state of development has recently obtained additional evidence from another approach: Bond and associates[2] have studied desoxyribonucleic acid synthesis in blood cells of the peripheral blood from normal human beings, using tritium-labeled thymidine. They found that 0.4 to 0.7 per cent of the large mononuclear cells are labeled, that is, are synthesizing desoxyribonucleic acid in preparation for the next mitosis. Labeling was only found in large mononuclear cells. This is in keeping with earlier work,[7] suggesting that mononuclear cells only are capable of further development.

MacDonald,[9] after labeling the cells with tritiated thymidine, finds most of the labeling during the first 72 hours in lymphocytes and mononuclear cells,

Fig. 1.

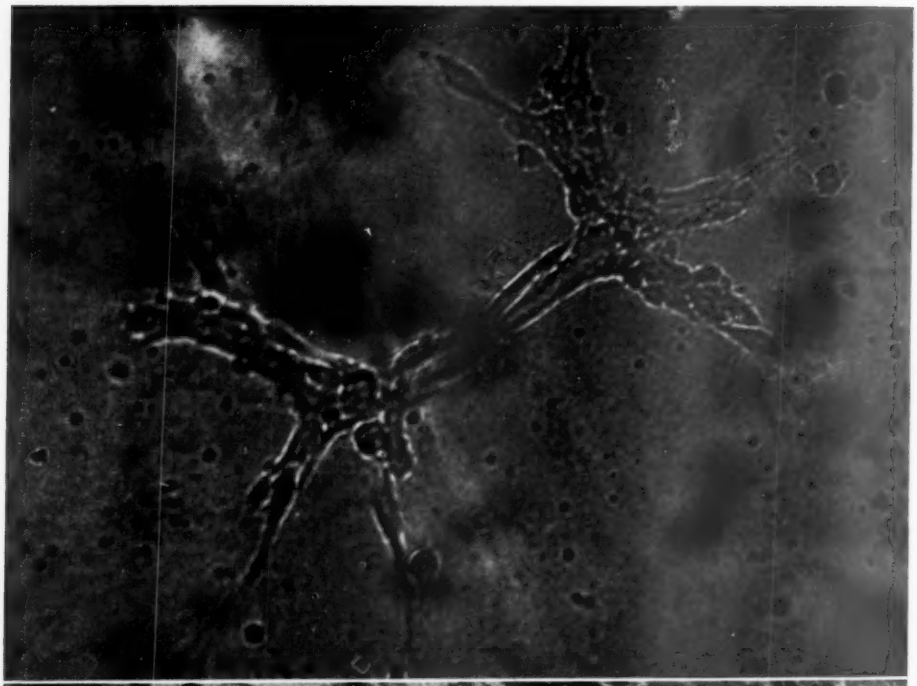

Fig. 2.

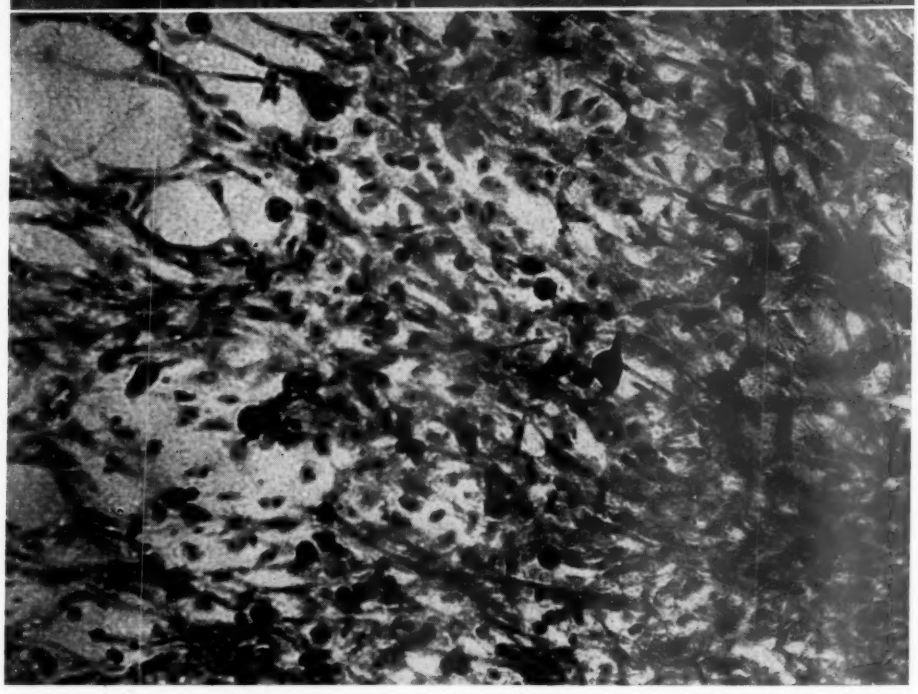

Fig. 1.—Small cell colony (probably arisen from one cell).

Fig. 2.—Transformed culture of buffy coat after 29 days in vitro (some mobile round cells are still present).

whereas later on labeling is more marked in the so-called fixed undifferentiated connective tissue cells. This, to our mind, would speak more in favor of transition from one to another than against it. It has been shown[1] that emigration of round cells is most active during the first 48 hours, whereupon the emigrated and local cells enter into mitosis. There are no morphologic criteria to tell one from the other. It seems obvious that all these actively dividing cells will be labeled. Presence of tritiated thymidine in a fibrocyte therefore in no way proves his origin from another local fibrocyte. Time-lapse cinematography shows transition from the mobile monocyte into the sessile fibrocyte to occur usually after cell division and to take place within a matter of minutes.

It is clearly crucial to an experiment concerned with the transformation of one cell type into another that contamination by the type of cells which is held to arise de novo be excluded. In cardiac puncture one cannot exclude the possibility that a plaque of tissue could be taken by the needle from the chest-wall or the myocardium. The results of repeated cardiac punctures in exsanguinated animals gave 11 individual cultures per 40 cardiac punctures. This would suggest that contamination could possibly account for one or two cultures per heart puncture, but could not yield up to 37 cultures as observed in one of the experiments reported in this paper.

Cannulation of the carotid artery with siliconed polyvinyl tubings reduces the chances of picking up tissue fragments of the integument to a great extent. Especially since the first blood sample was discarded before taking a sample for buffy coat preparation. Formation of fibrocytic proliferation occurred more frequently in carotid blood than in blood obtained by cardiac puncture.

The shape of cells is determined to a considerable degree by environmental conditions. A "free" fibroblast rounds off. In general, identification of single cells by morphologic criteria may be useful in a known tissue environment, but in culture morphology is at best an unreliable guide and functional capacities are of greater significance.

This is of particular importance in wound healing. Much of the difference of opinion as to the possibility of the formation of fibrocytes from white blood cells is due to the fact that the morphology of these cells is not as specific as to permit general agreement as to identification.

We have shown that monocytes can produce a collagen constituent in culture and it seems probable that they may also do so in wounds and thus be "functional" fibrocytes.

SUMMARY

Cultures from blood buffy coat of the rabbit have been found to transform and proliferate as fibrocytes. Cultivated over a period of 28 days such cultures form considerable amounts of hydroxyproline, an amino acid found in quantity only in connective tissue fibers. It is concluded that mononuclear cells of the blood are capable of transforming into functional fibrocytes. The importance of this fact for wound healing processes is discussed.

We are indebted to Dr. D. W. James, Dept. of Anatomy, University College, London, for his suggestions which stimulated the work included in this paper.

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THE USE OF RADIOACTIVE IODINE IN THE EVALUATION OF THYROID NODULES

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NUMEROUS reports attest to the frequent occurrence of thyroid cancer in nontoxic thyroid nodules.[2, 3, 11, 13, 19] The reported incidence of carcinoma in single nodules varies from 4 to 24.5 per cent and in multinodular glands from 3.4 to 12.8 per cent. In our own experience with 362 nontoxic nodular thyroid glands operated upon, 12.5 per cent of solitary and 4.7 per cent of multiple thyroid nodules revealed invasive carcinoma.

Because of the large number of benign nodules which must be removed in order to avoid missing a carcinoma, any method which would aid in the differentiation of benign from malignant thyroid nodules would be welcome. The clinical differentiation of benign from malignant nodules of the thyroid gland is often difficult or impossible. Although Crile[4] has claimed the unique ability to diagnose carcinoma preoperatively in 97 per cent of his cases, most observers can make the diagnosis accurately in only about one-fourth of cases. The classical signs of thyroid cancer—hardness and irregularity of the gland, fixation to surrounding structures, and vocal cord paralysis—are late findings and may sometimes be present in benign conditions. Hardness and irregularity may be found in chronic thyroiditis and in cases of nodular goiter with calcification. The simultaneous occurrence of carcinoma and calcification has been reported and we have seen it in three of our own cases. Fixation of the gland may be found in thyroiditis, but is otherwise a dependable sign of cancer. We have observed two instances of vocal cord paralysis caused by benign thyroid adenomas.

The importance of early diagnosis of thyroid cancer is evident from the report of Ward[18] who showed that when the diagnosis of cancer was made preoperatively the 5-year survival rate was only 20 per cent; if the lesion was considered benign clinically but was diagnosed grossly as carcinoma at operation, the 5-year survival rate was 40 per cent; if the diagnosis could only be made microscopically, 80 per cent of the patients survived 5 years.

In 1939 Hamilton and Soley[10] noted that malignant thyroid tissue picked up only a small fraction of ingested radioactive iodine as compared to normal thyroid tissue. Dobyns and associates[7] studied a large number of patients possessing thyroid nodules and determined the relative amount of ingested radioactive iodine picked up in the nodule as compared with the amount concentrated in the remainder of the thyroid gland. They were able by this technique to classify thyroid nodules into "cold," "warm," or "hot," depending on whether their respective uptake was less than, about the same as, or

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more than that of the nonnodular thyroid tissue. In a preliminary study, they found that none of the 119 thyroid cancers evaluated in this manner picked up a larger portion of radioactive iodine than the surrounding thyroid tissue.[6] Means[14] later reported that he had never seen a "hot" nodule that showed evidence of malignancy. These early studies seemed to indicate that a diagnostic procedure was available for differentiating between benign and malignant thyroid nodules, based upon their activity for radioactive iodine as compared to the nonnodular thyroid tissue. Further reports appeared to support the value of the test. Johnson and Beierwalters[12] found that 31 per cent of 32 patients with "cold" nodules had carcinoma of the thyroid, 10 per cent of 10 patients with "warm" nodules had cancer, and neither of two "hot" nodules was malignant. Perlmutter and Slater[16] studied 140 solitary nodules—of 99 "cold" nodules, 23 were malignant, whereas only one of 41 "hot" nodules was malignant (this patient had a previous total thyroidectomy for cancer, and the "hot" area was in a metastatic node). Groesbeck[9] reported on 237 patients operated upon for nodular thyroids who had prior study of the glands with radioactive iodine. He found cancer in 14.2 per cent of nonfunctioning nodules, 3.6 per cent in functioning ("warm") nodules, and in none of the hyperfunctioning nodules. It became apparent that the directional Geiger counter or scintigram for the differential study of thyroid nodules was a valuable diagnostic tool in the investigation of nodular thyroid glands.

Beginning in January, 1956, most of the patients seen with solitary or discrete thyroid nodules were subjected to differential study of the thyroid gland after ingestion of tracer doses of I^{131}, using either a lead-encased Geiger counter for directional counts or an automatic scintiscanning apparatus for evaluating the I^{131} pickup in the nodules as compared to the nonnodular thyroid tissue. From Jan. 1, 1956, through June 30, 1959, 148 patients with solitary or discrete nodules were operated upon (Table I).

TABLE I

ISOTOPIC FUNCTION	NUMBER OF PATIENTS	NUMBER OF CARCINOMAS	PER CENT OF CARCINOMAS
"Cold"	63	15	24.0
"Warm"	28	1	3.6
"Hot"	16	2	12.5
Not studied with I^{131} tracer	41	4	9.7
Total	148	22	14.9

Twenty-two of the 148 patients with solitary or discrete thyroid nodules proved to have carcinoma. Of 41 patients not studied with I^{131}, 4 proved to have carcinoma. One hundred and seven patients were evaluated with radioactive iodine pickup studies. Fifteen of the 63 "cold" nodules were malignant (24 per cent), one of the 28 "warm" nodules was malignant (3.6 per cent), and 2 of the 16 "hot" nodules were carcinomas (12.5 per cent). The scintigram of one of the patients in whom a "hot" nodule proved to be malignant is shown in Fig. 1.

The results in this limited series of cases would seem to indicate that the use of radioactive iodine pickup studies for differentiating between benign and malignant nodules of the thyroid gland is not wholly reliable. Dobyns and Maloof[6] stated that they had found a thyroid cancer in another part of a thyroid gland that contained a "hot" nodule. Cattell[1] reported the case of a physician with a nodule which picked up eight times as much iodine as the rest of the gland, and who was found at operation to have a carcinoma of the thyroid invading the trachea. It is probable that the incidence of cancer in "hot" thyroid nodules is much lower than the 12.5 per cent we found in our series, since a large number of patients with "hot" nodules were not treated or given thyroid hormones and not referred for surgical treatment. Nevertheless, we feel that finding cancer in two patients with "hot" nodules indicates the fallibility of the test as a diagnostic tool. The finding of carcinoma in a hyperfunctioning nodule may be due to one of three causes: (1) the carcinoma may be a functioning follicular carcinoma with great avidity for iodine; (2) the "hot" nodule may be a benign adenoma which obscures a neighboring nonpalpable carcinoma (about one-third of clinically solitary nodules prove to be multiple at operation); or (3) the thyroid tissue immediately surrounding a nonfunctioning carcinoma may be hyperfunctioning, and pick up more iodine than the remaider of the gland.

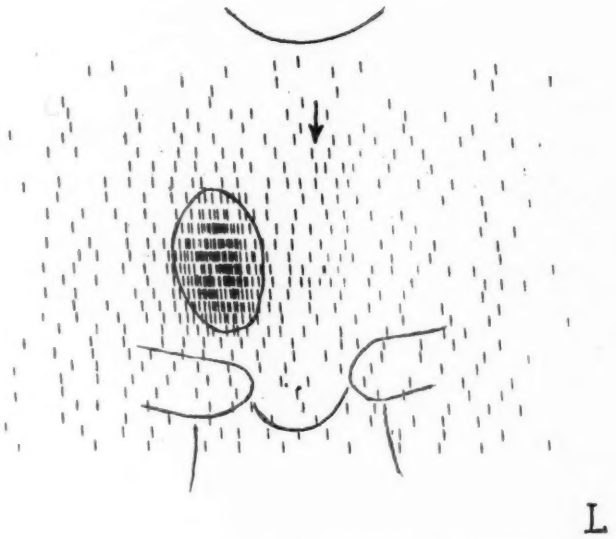

Fig. 1.—"Hot" nodule which proved to be papillary carcinoma at operation.

My present approach to the problem of the nontoxic thyroid nodule is as follows: If the thyroid gland is diffusely enlarged and smooth, or diffusely nodular, surgery is indicated only for the relief of pressure symptoms, tracheal deviation or compression, or substernal extension of the goiter. If a solitary or dominant nodule is present, I^{131} studies are performed. In patients under 25 years of age (highest cancer incidence) and in those with clinical evidence of neoplasia, such as hardness and irregularity, fixation and/or hoarseness associated with vocal cord paralysis, surgery is performed regardless of the

results of laboratory investigation. In the remaining patients, the nodules are classified as "hot" (hyperfunctioning), "warm" (functioning), and "cold" (hypofunctioning). All "warm" and "cold" nodules are operated upon without delay and a total thyroid lobectomy on the involved side is performed. The "hot" nodules which are clinically benign are given a therapeutic trial of TSH-suppression, using either thyroid extract (0.06 to 0.2 Gm. daily), or tri-iodothyronine (75 to 100 mcg. daily) for about 3 months. If the nodule disappears or diminishes markedly in size, surgery is not performed. There are several reports of the successful use of thyroid hormone in the management of benign nodular goiters.[8, 16] All persistent nodules are surgically extirpated. There is some evidence that certain thyroid cancers may regress following the use of thyroid hormone.[5, 17] In the one "warm" thyroid nodule in our series which proved to be a follicular carcinoma at operation, there was about 25 per cent reduction in the size of the nodule after 5 months of thyroid extract administration.

ADDENDUM

Since this paper was submitted for publication, I have encountered an additional case in which a "hot" nodule of the thyroid gland proved to be a papillary carcinoma of the thyroid upon removal.

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THE DIAGNOSIS OF THYROID CANCER WITH RADIOACTIVE PHOSPHORUS

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ALTHOUGH thyroid cancer occurs in a significant number of solitary nodular goiters and multinodular goiters, there is no consistently accurate method of diagnosing cancer in these cases. While physical examination and the radioactive iodine uptake test point out suspicious lesions, there is no specific test for thyroid malignancy. In this preliminary report a diagnostic test for thyroid cancer employing radioactive phosphorus (P^{32}) uptake is described, in which the uptake of the suspicious area is compared with that of surrounding areas in the neck. This test is based on the known increase of phophorus metabolism that occurs in neoplastic tissue.

METHOD

Twenty-nine patients were evaluated by the radiophosphorus uptake test. These patients, who included 21 women and 8 men with an age span of 19 to 73 years, were from the outpatient and inpatient services of the University of Minnesota Hospitals, and all had solitary or multiple thyroid nodules.

Approximately 24 hours before counting 500 microcuries of phosphorus^{32} (P^{32}) was administered orally as sodium phosphate to the patients. Counting was carried out with an eye probe Geiger-Mueller tube (Anton Laboratories Model 222). Background counts averaged 10 c.p.m. and counts over normal thyroid averaged 115 c.p.m. At least 3 one-minute counts and as many as 26 counts were taken over the nodular area by manually holding the G-M tube directly over this area with firm pressure. Surrounding thyroid and anterior neck tissues were used as a control and were counted in a similar manner.

Since P^{32} is exclusively a beta emitter, it is preferable to perform this test before the I^{131} uptake test. However, when the time interval after the I^{131} test exceeded 3 weeks, the residual activity in the thyroid was small enough to enable the performance of the P^{32} uptake test. The I^{131} activity was treated as part of background and subtracted from total P^{32} activity. Since the I^{131} uptake test involves counting gamma rays, it is possible to perform this test immediately after the P^{32} uptake test.

RESULTS

In this group of 29 patients studied, there was a distinct dividing line between the positive and negative tests. The ratio of uptake of P^{32} in the suspicious tissue as compared with normal tissue ranged from less than 1 to 1.12

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in the negative studies, while this ratio ranged from 1.33 to 1.61 in the positive tests (Fig. 1). Twenty-three patients fell into the negative range, while 6 patients were judged positive. All but 8 of the 23 negative cases were operated upon. The remaining 8 patients were not explored for a variety of reasons (Table I). Several of these patients had other conditions of greater severity which precluded the possibility of thyroid surgery, including liver abscess and septicemia, coronary heart disease, carcinoma of the colon, and cerebrovascular accident. The diagnoses in other patients were clinically benign and permission for surgery was denied. In the other 15 cases with a negative P^{32} uptake, microscopic diagnoses were obtained (Table II). Most of these lesions consisted of benign adenomas. In the one false negative study, the initial microscopic impression was that of benign tissue. However, several small separate nodules were found in the midline of the neck which showed on microscopic section the identical type of benign-appearing thyroid tissue (Fig. 2).

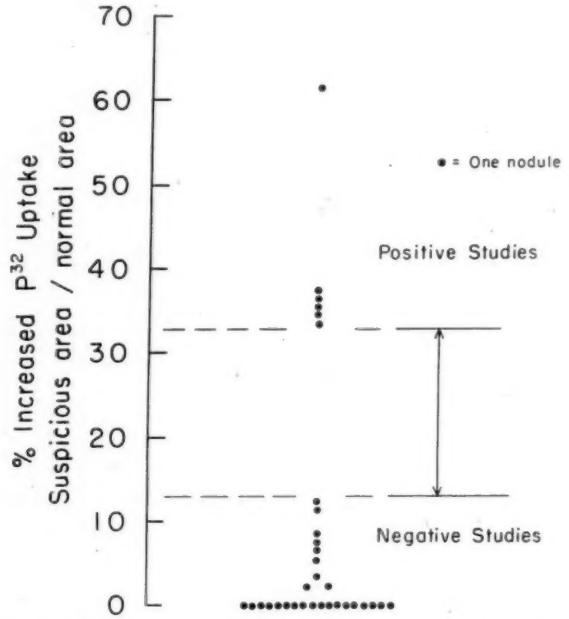

Fig. 1.—A distinct dividing line exists between positive and negative P^{32} uptake tests.

TABLE I

PATIENTS	AGE (YEARS)	SEX	P^{32} UPTAKE: SUSPICIOUS AREA/NORMAL	REASON FOR NONOPERATIVE MANAGEMENT
6	28-71	4M 4F	Mean 0.93 Range 0.81 to 1.11 S.D. 0.09	Severe concurrent disease—5 cases Obviously benign clinically—3 cases

TABLE II

PATIENTS	AGE (YEARS)	SEX	P^{32} UPTAKE: SUSPICIOUS AREA/NORMAL	MICROSCOPIC DIAGNOSIS
15	19-73	2M 13F	Mean 0.98 Range 0.85 to 1.12 S.D. 0.07	Benign lesions—14 cases Well-differentiated follicular carcinoma—1 case

There was no evidence of lymphoid tissue in these nodules. A re-examination of the thyroid revealed a homogeneity of microscopic appearance throughout the gland (Fig. 3). Because of the isolated nodules the thyroid tissue was called an exceptionally well-differentiated follicular carcinoma. In 5 of the 6 cases with positive P^{32} uptake tests, malignancies were discovered on surgical exploration (Table III). The one false positive test consisted of a very cellular Hashimoto's thyroiditis which was not diagnosed preoperatively (Fig. 4). The 5 malignant tumors included a rare malignant lymphoblastoma of the thyroid (Fig. 5) and a Hürthle cell carcinoma. An anaplastic carcinoma (Fig. 6) and a tumor composed predominantly of follicular carcinoma with some papillary elements were also in this series. The fifth tumor was a large highly suspicious mass in the region of the thyroid gland. A small biopsy in the lateral aspect of the tumor was performed without an adequate exploration of the neck. Microscopic report revealed "malignant tumor of neck, possibly metastatic" (Fig. 7). The patient was treated by external radiation and is still alive at present.

TABLE III

PATIENTS	AGE (YEARS)	SEX	P^{32} UPTAKE: SUSPICIOUS AREA/NORMAL	MICROSCOPIC DIAGNOSIS
6	30-73	3M 3F	Mean 1.36 Range 1.33 to 1.61 S.D. 0.09	Malignant lesions—5 cases Anaplastic carcinoma of thyroid Hürthle-cell carcinoma of thyroid Follicular carcinoma of thyroid Malignant lymphoblastoma of thyroid Malignant tumor of neck, possibly metastatic Hashimoto's thyroiditis—1 case

DISCUSSION

The incidence of thyroid cancer in nontoxic nodular goiter varies in different series, but is significant enough for one to view these goiters clinically with suspicion.[2] In solitary nodular nontoxic goiters the incidence is even higher, varying in the series of Lahey,[8] Cole,[10] and Cope[3] from 10 to 25 per cent. Cancer is less common in multinodular nontoxic glands, but even in this group there is a significant incidence. Pertinent points in the history of the goiter and in the physical examination, such as sudden appearance of the nodule, progressive increase in size, relative fixation, irregular shape, and hardness of the nodule may increase the suspicion of cancer, but these are not entirely reliable signs and may be associated with benign lesions. The symptoms of hoarseness, dysphagia, and stridor are significant but occur late in the disease. The radioactive iodine uptake test has been of some value in the diagnosis of thyroid cancer since most of the cancers occur in "cold" nodules, that is, nodules with decreased uptake. However, colloid cysts and necrotic and nonfunctioning adenomas are also "cold" nodules.[4] Accuracy in glands with small nodules is decreased. In Beierwaltes' series,[5] over 25 per cent of "cold" nodules were

Fig. 2.

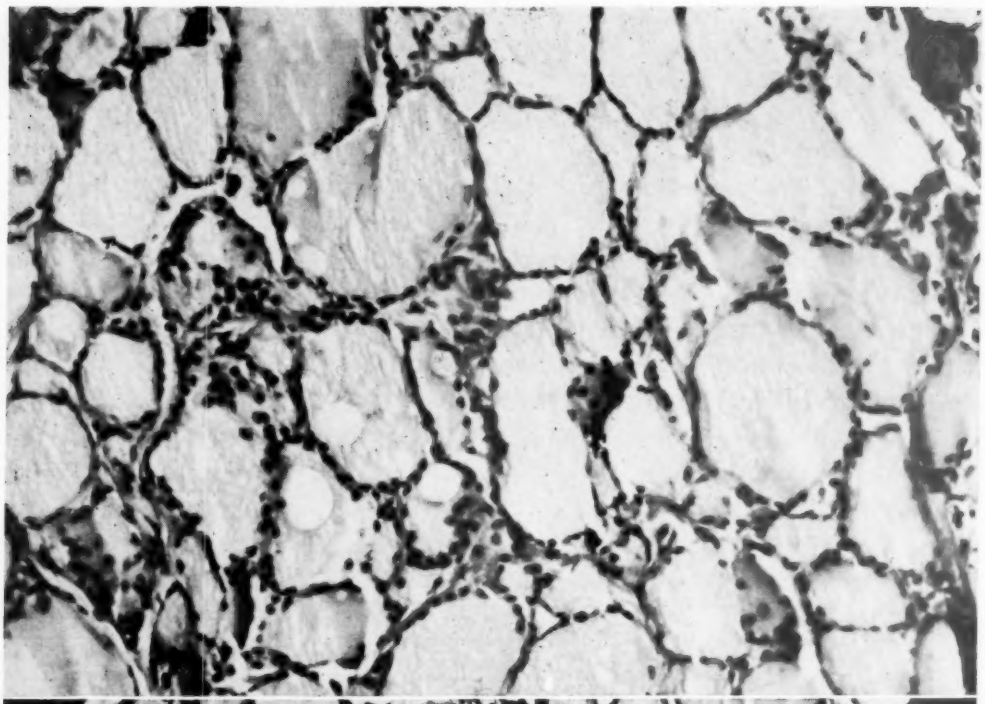

Fig. 3.

Fig. 2.—Well-differentiated follicular carcinoma in discreet nodule of neck. (×210.)

Fig. 3.—Well-differentiated follicular carcinoma of the thyroid giving false negative P^{32} uptake test. (×135.)

Fig. 4.

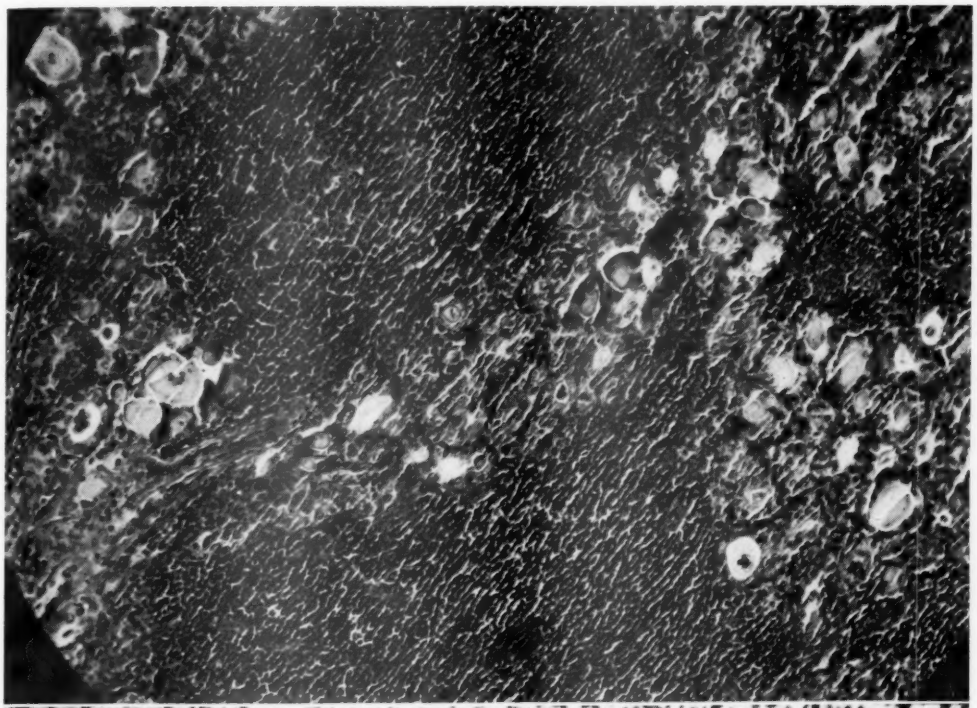

Fig. 5.

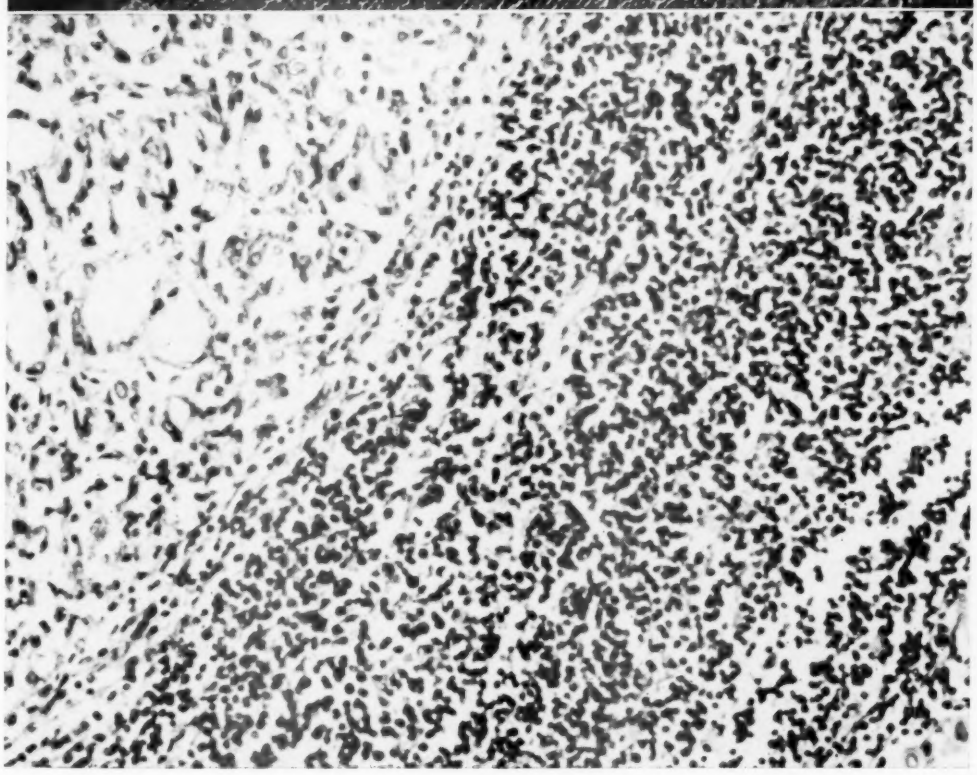

Fig. 4.—Hashimoto's thyroiditis giving false positive P^{32} uptake test. (×135.)
Fig. 5.—Malignant lymphoblastoma of the thyroid. (×210.)

Fig. 6.

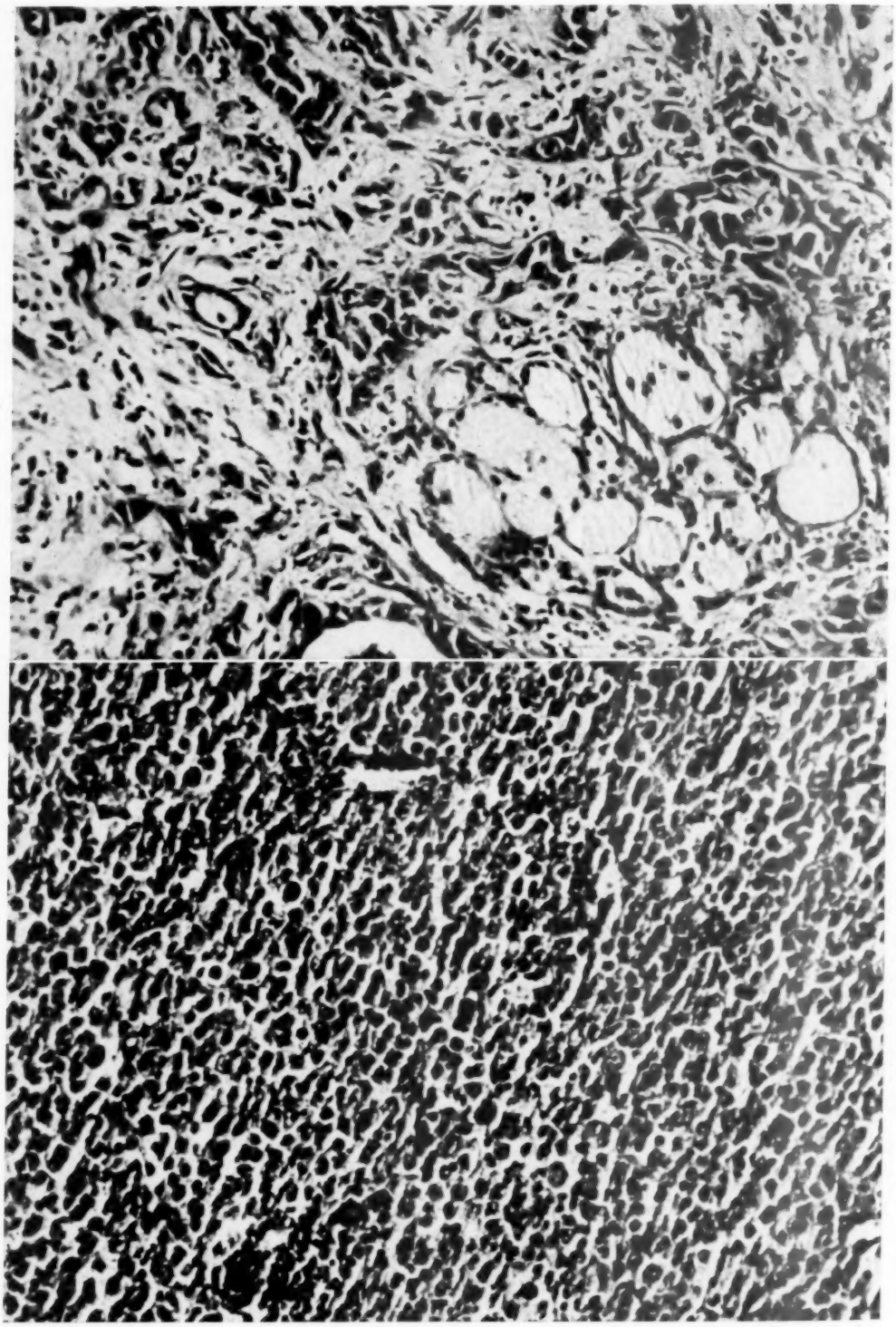

Fig. 7.

Fig. 6.—Anaplastic carcinoma of the thyroid. (×210.)
Fig. 7.—Malignant tumor of neck, possibly metastatic. (×210.)

proved to be carcinomas. Carcinoma of the thyroid occurs on rare occasions in the "warm" nodules, that is, nodules that concentrate I^{131} at the same rate as surrounding normal thyroid tissue. Thus a test with more accuracy than the I^{131} uptake would be of value.

It has been known for some time that P^{32} uptake and metabolism are increased in neoplastic tissue.[6, 11] This increased P^{32} uptake has formed the basis of clinically useful tests in diagnosing cancers of the brain[13] and of the eye.[7] Cancers of the breast,[9] stomach and esophagus,[12] and skin,[1] as well as other organs, have been studied by P^{32} uptake. An important consideration limiting the use of phosphorus is that P^{32} is a beta ray emitter exclusively and that the maximum depth of penetration through soft tissue is 8 mm. Most lesions of the thyroid gland are fairly superficial and permit the use of P^{32} for uptake studies. In a recent study on excised thyroid tissue, Thomas[14] demonstrated that thyroid/serum ratios of P^{32} content were over twice as high in cancerous tissue than in normal and nonmalignant thyroid tissue. In the present study with a small group of patients, results of the thyroid P^{32} uptake test have proved promising. Because of the natural limitations of the test it is felt that small and deep-seated lesions may be missed. The test is more easily performed where the nodules are discreet from the surrounding tissue. It is more accurately performed when the patient has not had a recent I^{131} test since subtraction of the gamma ray counts adds another source of error. Size of the goiter alone does not influence test results since the largest goiter studied occurred in a benign case. Two of the cancers were also fairly large in size. Inflammatory lesions, such as Hashimoto's thyroiditis and subacute thyroiditis, may give positive results due to increased cellularity and metabolic activity. These lesions, however, represent a small percentage of nodular goiters. The false negative test in this series represented histologically a well-differentiated low grade malignancy. One may speculate that this tumor may be, in addition, low grade metabolically. Clinically, the goiter had been present for many years and there was no evidence of spread outside the neck, or through the thyroid capsule itself. Among the positive tests there is no significant differentiation in P^{32} uptake between the different types of malignancies, except for the greatly increased uptake of the anaplastic carcinoma. This lesion was a very rapidly progressing cancer to which the patient succumbed within 4 months. Its higher metabolic activity may well have been responsible for the very high P^{32} uptake.

CONCLUSION

A test employing radioactive phosphorus uptake for the diagnosis of thyroid cancer in solitary nodular and multinodular goiter has been described.

In 29 cases studied, 6 positive and 23 negative tests occurred. Five of the 6 positive cases were malignant, with the one exception proving to be a highly cellular Hashimoto's disease. Of the 23 negative studies, 15 were operated upon. Fourteen of these were benign and one was an exceptionally well-differentiated follicular carcinoma. The 8 patients not operated upon were felt to be benign clinically. The potential advantages and disadvantages of this test are discussed further.

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HEALING POTENTIAL OF THE PHARYNX AND CERVICAL ESOPHAGUS

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NECK surgery often necessitates removal of portions of the pharynx and cervical esophagus, and in some instances removal of the entire swallowing organ from the base of the tongue to the arch of the aorta. It is the responsibility of the surgeon to reconstruct the surgical defect so that normal function may be re-established.

Reconstruction of a tube for swallowing may be accomplished by utilizing the remaining portions of the pharyngeal and esophageal wall. If the reconstruction results in a markedly narrowed tube, some advocate the use of split-thickness skin to increase the caliber of the reconstructed organ. In those instances which require complete removal of the pharynx and the cervical esophagus, reconstruction is usually accomplished by means of a split-thickness skin graft over a tantalum mesh cone sutured between the base of the tongue and the thoracic esophagus. Less often, skin flaps from the neck or chest wall are fashioned into tubes to bridge the defect.

Although the over-all results have been functionally satisfactory, a better understanding of certain clinical observations was considered important in evaluating the methods of repair.

1. Removal of the larynx and portions of the pharynx with subsequent reconstruction performed by suturing together the edges of the defect in tubular fashion resulted in a high incidence of esophagocutaneous fistulas. In one series of operations (total laryngectomy and radical neck dissection), fistulas occurred in 45 per cent of patients. In spite of this very high incidence, well over 95 per cent of these fistulas healed spontaneously without stricture formation or dysfunction. Only in rare instances was it necessary to perform surgical closure. This suggested that these tissues had a strong natural healing tendency.

2. An intact strip of pharyngeal or esophageal wall no greater than 1 cm. in width in the relaxed state was adequate for reconstruction of a functional swallowing organ. In practice, if the remaining strip could be closed over a No. 16 nasogastric tube without tension, an adequate functional result could be expected. This suggested that these organs could compensate for large losses of tissue substance.

3. The use of a partial skin graft to increase the caliber of the pharynx usually resulted in marked contracture of the graft. The addition of such a graft appeared to produce no better functional result than did primary closure of the mucosal edges.

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4. In many instances, total excision of the pharynx and cervical esophagus with a skin graft reconstruction to bridge the defect resulted in stricturing, especially at the esophageal junction. Many of these patients required periodic dilatation to keep the caliber of the lumen large enough to admit a 36 to 40 F. bougie. In comparison, the pharyngeal tubes reconstructed with a strip of pharyngeal and esophageal wall just sufficient to close over a No. 16 nasogastric tube rarely required dilatation, and eventually compensated for additional stress so that patients could take a fairly normal diet. This suggested that the contractile nature of split-thickness skin was functionally less satisfactory than even a narrow strip of esophageal or pharyngeal wall.

In view of these observations, it was considered worth-while to study the normal healing and compensatory powers of the pharynx and cervical esophagus.

Fig. 1.—Operative field showing the open strip of pharyngeal-esophageal mucosa. "The esophageal strip was left open, with no attempt at repair, and without a nasogastric tube, prosthesis, or stent to act as a guide for tubulation."

METHOD

Surgery under general anesthesia was performed on 14 dogs. The esophagus was exposed through a midline incision in the neck. An 8 by 10 cm. segment of cervical esophagus was partially resected, removing more than three-fourths of the circumference of the esophageal wall, leaving a posterior strip not more than 1 cm. in width and at least 8 cm. in length (Fig. 1). The esophageal strip was left open, with no attempt at repair, and without a nasogastric tube, prosthesis, or stent to act as a guide for tubulation. A Penrose drain was inserted into the neck wound and then sutured to the skin to allow the saliva to drain from the operative site. A gastrostomy was performed for feeding purposes.

The dogs received subcutaneous fluids during the first 36 hours. Gastrostomy feedings were started on the second postoperative day, and consisted of clear liquids for the first 24 to 48 hours and dog food with bouillon thinned with water thereafter. Penicillin and streptomycin were administered subcutaneously for 5 days.

RESULTS

Two of the dogs died within the first 3 postoperative days. Autopsy revealed no specific reason for these deaths, and they were attributed to anesthesia, postoperative depression, and possibly shock. One of the dogs died of pneumonia on the twenty-fifth postoperative day. Four more dogs died between the second and the fourth weeks as a result of electrolyte imbalance after leaking gastrostomy tubes had produced considerable loss of stomach juices and inanition. In no instance did a dog die of mediastinitis.

By the third or fourth day in most instances, the animals were alert, showed an interest in their surroundings, and sought attention when someone approached the cage.

The neck wound was healed in 7 to 14 days. Oral feedings were started between the fifteenth and twenty-fifth days. Early during the experiment, the gastrostomies were maintained for as long as 49 days, but later it was found that the dogs progressed more favorably if the gastrostomies were closed as soon as the animals showed ability to take adequate amounts of nourishment by mouth. In most instances, the dogs lost a few kilograms of weight postoperatively. As soon as oral feedings were started, however, the animals began to gain weight (Table I).

TABLE I. SPONTANEOUS TUBULATION

DOG NUMBER	DAYS ALIVE (P.O.)		NECK HEALED (P.O. DAY)	FEEDINGS STARTED (P.O. DAY)	GASTROSTOMY OUT (P.O. DAY)	TUBULATION COMPLETE
47	2	P.O. death	No	No	No	No
169	3	P.O. death	No	No	No	No
153	10	Died	No	No	No	No
128	14	Died	8	No	No	Yes
112	15	Died	No	No	No	No
44	25	Died	5	15	21	Yes
162	27	Died	13	18	No	Yes
166	105	Sacrificed	7	21	30	Yes
77	168	Sacrificed	15	19	42	Yes
189	273	Sacrificed	7	16	15	Yes
92	370	Sacrificed	11	14	24	Yes
37	420	Sacrificed	12	25	49	Yes
196	424	Sacrificed	9	16	15	Yes
81	521	Sacrificed	14	15	14	Yes

P.O.—Postoperative.

Roentgenographic Findings.—Esophagrams were taken at 15 and 30 days, and at 2, 3, and 6 months (Figs. 2, 3, and 4). An adequate tube was demonstrated in some of the dogs as early as the fifteenth day. There appeared to be no dysfunction and there were no areas of stricture. At 6 months, it was difficult to distinguish the segment of esophagus operated upon from the remaining portion of this organ.

Fig. 2.

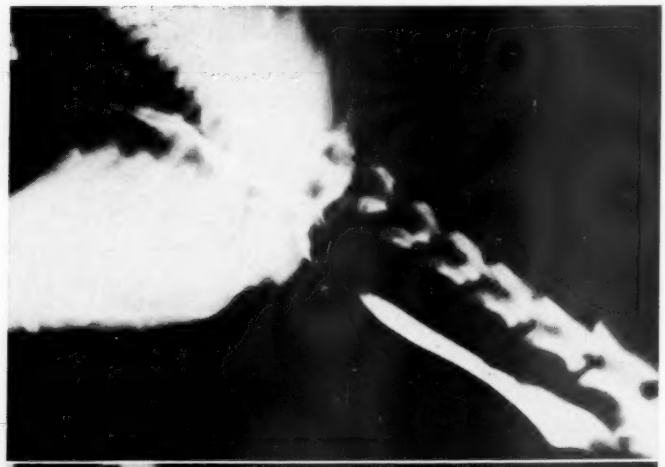

Fig. 3.

Fig. 4.

Fig. 2.—Esophagrams 15 days after surgery.
Fig. 3.—Esophagrams 40 days after surgery.
Fig. 4.—Esophagrams 5½ months after surgery.

Gross Findings.—Autopsies showed that the esophageal strip had formed a completely closed tube continuous with the remaining segments of the pharynx and esophagus. In one animal that died on the fourteenth day, spontaneous tubulation had already occurred.

Dogs sacrificed at 1 month following surgery showed complete tubulation. The anterior wall of the operated segment comprising 50 to 60 per cent of the circumference of the tube appeared grossly as thin, membranous, and somewhat transparent tissue. The tube was distensible to the caliber of the distal normal esophagus.

Dogs sacrificed at 3 months showed diminution of the membranous segment to approximately one-fourth of the circumference of the tube. The caliber of the segment of esophagus operated upon was distinctly smaller than the segment distal to it. The tube, however, was soft, pliable, and distensible.

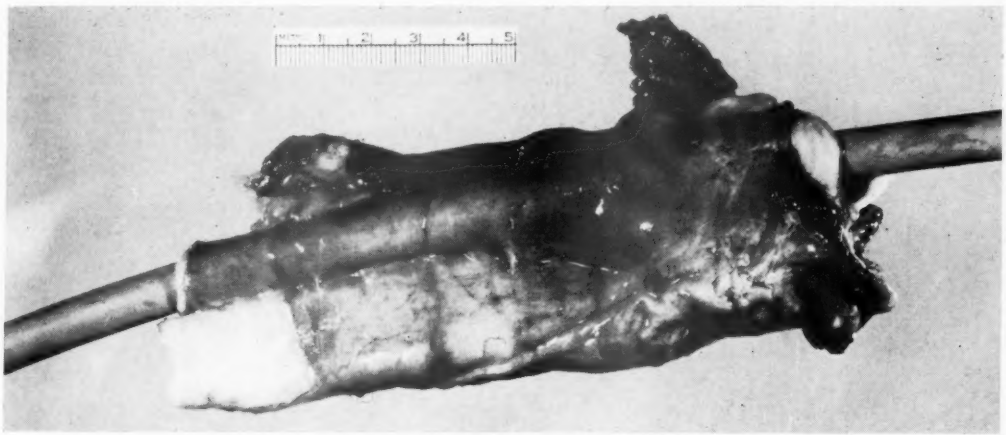

Fig. 5.—Specimen removed from dog sacrificed 5½ months after surgery.

At 6 months, the membranous tissue could no longer be identified. The segment of the esophagus operated upon was distinctly smaller in caliber than the proximal pharynx and distal esophagus, and its diameter measured approximately one-half the diameter of the dog's normal esophagus. The thickness of the wall of the segment operated upon, however, was the same as the normal esophagus. The tube was soft and pliable and could be distended with ease to half again its diameter (Fig. 5).

There were no areas of stricturing, fibrosis, or abscess formation.

Microscopic Findings.—Histologic sections from these newly formed tubes were studied at 25 days, 3½ months, and 5½ months.

The histologic sections at 25 days showed a completely closed tube. Approximately one-half the circumference of the tube consisted of normal esophageal wall, and all layers (mucosa, submucosa, and muscle layers) could be identified. This portion, no doubt, represented the posterior strip which was left in place at operation. The remaining segment of the tube consisted of an inner layer of stratified squamous epithelium continuous with the stratified squamous epithelium of the normal segment. The outer layer, which formed

Fig. 6.

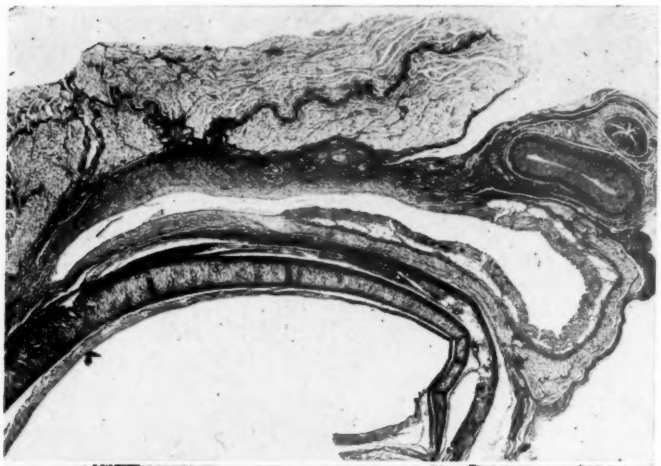

Fig. 7.

Fig. 8.

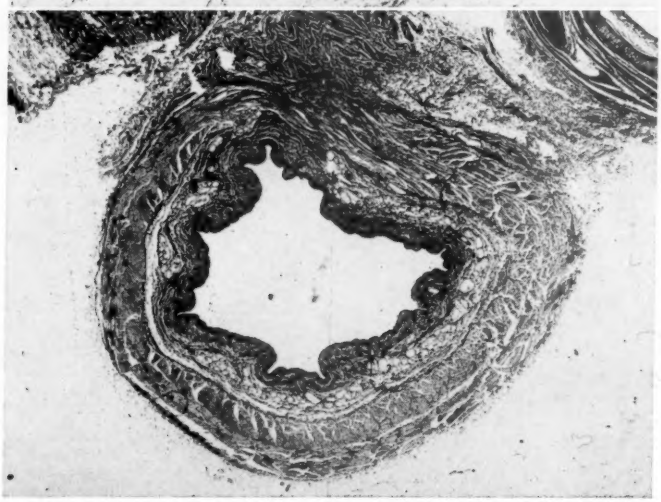

Fig. 6.—The cross section of a tube 25 days after surgery. The normal esophageal wall is readily recognized circling half of the new tube.

Fig. 7.—The cross section of a tube 3½ months after surgery. The fibrous segment has diminished considerably. The squamous epithelium in this area appears to be folding upon itself as a result of the contraction of the outer layer of fibrous tissue.

Fig. 8.—The cross section of a tube at 5½ months. The fibrous segment is even smaller.

90 to 95 per cent of the thickness of the wall in this area, consisted of fibrous tissue (Fig. 6). It was this fibrous segment which appeared as the membranous portion described.

At 3½ months, the fibrous segment formed 20 per cent of the circumference of the tube. Histologically, the layers were the same (Fig. 7).

At 5½ months, the fibrous segment measured 1/13 or 7 per cent of the circumference of the tube (Fig. 8).

DISCUSSION

The findings in these experiments indicated that the pharynx and esophagus of the dog have a tremendous potential to re-establish a functional swallowing organ. Fistulas, even large ones, healed spontaneously, provided that the nutritional status of the animal was maintained and that infection, abscess formation, and mediastinitis were prevented.

Fig. 9.—Dog one year after surgery maintaining adequate nutrition on oral feedings.

When a fistula existed, it appeared that the body quickly laid down fibrous tissue to wall off the secretions being carried by the pharynx and esophagus, much the same way as fibrous tissue is laid down to wall off an abscess. The epithelium from the mucosal edges of the posterior strip of pharyngeal and esophageal wall covered the inner surface of this fibrous tissue, forming a closed tube completely lined with stratified squamous epithelium. The outer fibrous tissue layer which originally formed a large partial circumferential segment of the new swallowing organ slowly contracted, drawing the edges of the original strip of pharyngeal and esophageal wall closer and closer together. Finally, over 90 per cent of the new swallowing organ was composed of normal esophageal wall, which represented the original strip of tissue left in place at

the time of surgery. This new organ had the ability to distend, and gradually compensated for additional stress, thus permitting adequate swallowing function (Fig. 9).

These experimental findings parallel the clinical findings previously mentioned, namely: (1) fistulas, even extensive ones, heal spontaneously; (2) even a very narrow strip of pharyngeal or esophageal wall will provide a functional organ for swallowing; and (3) these reconstructed tubes, though narrow in caliber, are capable of distension and hypertrophy, and can compensate for additional stress. Even a narrow strip of pharyngeal and esophageal wall will provide adequate function.

SUMMARY

It was found that a narrow open strip of cervical esophagus in the dog will undergo spontaneous tubulation. This occurred within 15 to 25 days, provided that the nutritional status of the dog was maintained. At the end of this period, the dog swallowed without difficulty and was able to maintain adequate nutrition. At autopsy, the narrow strip of mucosa was found to have developed spontaneously into a completely closed tube continuous with the remaining portions of the esophagus. This tube, though somewhat smaller in caliber than the remaining portions of the esophagus, was soft, pliable, and easily distensible. Histologic sections through this tube showed concentric layers of mucosa, muscularis mucosa, and muscularis externa throughout 95 per cent of the wall of the newly formed organ. The remaining 5 per cent of the tube consisted of an inner layer of stratified squamous epithelium and an outer fibrous tissue layer. These findings parallel clinical observations in human subjects.

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BASSINI'S CONTRIBUTION TO OUR UNDERSTANDING OF INGUINAL HERNIA

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BASSINI proposed an entirely new approach to the treatment of inguinal hernia, the anatomic approach. Before him the treatment consisted only of closing the hernia sac at the level of the subcutaneous ring.

Since Bassini's first publication in 1887,[2] a great deal has been written about his method. Unfortunately the great contribution of Bassini's work has been obscured by emphasis on his method of the repair of the posterior wall of the inguinal canal. Reconstructive repair is indeed important in the treatment of inguinal hernia but the great innovation of Bassini was in the initial steps of his operation: opening the inguinal canal, mobilization of the cord, and ligation and amputation of the sac at the deep inguinal ring.

Bassini wrote:* . . . He incises the skin and subcutaneous tissues of the inguino-scrotal region, and exposes the aponeurosis of the external oblique in an area which corresponds to the hernia opening. He isolates the spermatic cord and the neck of the hernia sac in relation to the underlying external inguinal ring. This represents the first stage of the operation.

In the second stage he divides the aponeurosis of the external oblique from the external inguinal ring to a point past the internal ring, and completely separates the spermatic cord from the neck of the hernia. Placing an index finger under these parts he isolates, with blunt instruments, the neck of the hernia sac from the elements of the cord up to where the neck joins the peritoneum. Here he places a ligature or suture of catgut and excises the sac distally.[3]

The third stage of the operation is the well-known repair of the posterior wall.

Bassini published his technique and the results achieved by it, and then apparently felt that the problem of inguinal hernia was solved. He wrote many surgical treatises but nothing about hernia after 1894.[1] He did not become involved in the controversies which followed his publications.

Bassini was the first to advocate the opening of the inguinal canal, the first to close the hernia sac at the deep inguinal ring, and the first to recognize the importance of the obliquity of the inguinal canal.

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*". . . Incide gl'integumenti della regione inguino-scrotale erniosa, e li disseca dall'aponeurosi del grande obliquo per il tratto di questa che corrisponde all'apertura dell'ernia. Isola il cordone spermatico ed il collo del sacco erniario nella porzione sottostante all'anello inguinale esterno.

Questo costituisce il primo momento dell'operazione.

Nel secondo momento taglia l'aponeurosi del grande obliquo dall'anello inguinale esterno fino al di la' dellinterno, e distacca in totalita' il cordone spermatico ed il colletto del sacco erniario. Tenendo l'indice sotto le dette parti, isola, cogl'instrumenti ottusi, il collo del sacco erniario, dagli elementi del funicolo, fino all'inboccatura dell'ernia. Quivi applica una legatura o sutura con catgut e recide il sacco erniario."

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HALSTED'S OPERATION FOR INGUINAL HERNIA. EXACTLY WHAT IS IT?

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WHEN new operative techniques are brought forth, various reactions may follow. Sometimes the new techniques are so much better than those preceding them that they find immediate widespread acceptance. Sometimes they prove to be of so little value that they shortly fall into oblivion, or they may give rise to a series of modifications, some approved and accepted, others disapproved and abandoned after a period of trial. Halsted's various methods of hernia repair were abandoned by him but have been followed by many even to the present time.

ORIGINAL METHOD

On June 13, 1889, Halsted performed his first operation for inguinal hernia by his original method. This case and four others were presented on November 4 of the same year to The Johns Hopkins Hospital Staff. He described his method as follows:

1. The incision begins at the external abdominal ring, and ends one inch or less (less than one inch in children) to the inner side of the anterior superior spine of the ilium on an imaginary line connecting the anterior superior spines of the ilia. Throughout the entire length of the incision everything superficial to the peritoneum is cut through.

2. The vas deferens with its vessels is carefully isolated up to the outer termination of the incision, and held aside.

3. The sack is opened and dissected from the tissues which envelop it.

4. The abdominal cavity is closed with quilted sutures passed through the peritoneum at a level higher by 1½ to 2 inches, than that of the so-called neck of the sack.

5. The vas deferens and its vessels are transplanted to the upper outer angle of the wound.

6. Interrupted, strong silk sutures, passed so as to include everything between the skin and the peritoneum, are used to close the deeper portion of the wound, which is sewed from the crest of the pubes to the upper outer angle of the incision. The cord now lies superficial to these structures and emerges through the abdominal muscles about one inch to the inner side of the anterior superior spine of the ilium.

7. The skin is united over the cord by interrupted stitches of very fine silk. These stitches do not perforate the skin, and when tied they become buried. They are taken from the under side of the skin, and made to include only its deep layers—the layers which are not occupied by sebaceous follicles.

LATER METHOD

In 1903 Halsted wrote that early in his work he used the Bassini technique together with his own to evaluate the difference in results. Of the cases treated

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by Bassini's method he says: "... all of the cases treated in this manner (cord undisturbed) remained cured."[2] In this paper he reports that he had abandoned his technique of transposing the cord subcutaneously. He had developed a further variation as to the handling of the inguinal cord:

> The lower flap of the cremaster muscle and its fascia is drawn up under the mobilized internal oblique muscle and held in this position by very fine silk stitches, which, having engaged firmly a few bundles of the cremaster, perforate the internal oblique, perferably where it is becoming aponeurotic, and are tied on the external surface of the latter (vide Fig. 1). . . . The external oblique muscle, mobilized and possibly further released by incising the anterior sheath of the rectus muscle, is stitched [the conjoint tendon also] to Poupart's ligament in the Bassini-Halsted manner.[2]

At the time of Halsted's first publication on hernia in 1889, there was little appreciation of the anatomy of the inguinal region. Hernia operations were carried out at the subcutaneous inguinal ring. Bassini's publication in 1887 was not generally known.

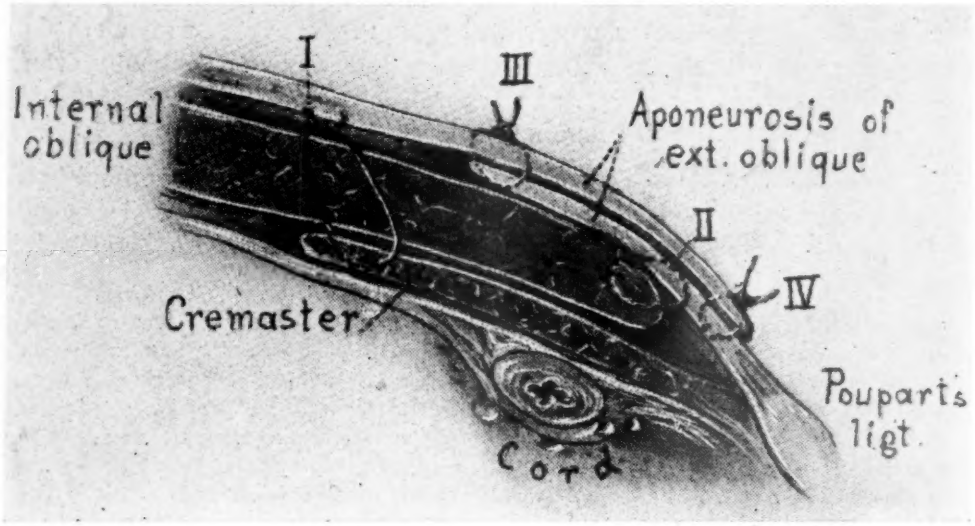

Fig. 1.—Position of the cord and cremaster muscle in relation to the internal oblique muscle. Sutures anchor the cremaster to the internal oblique and the internal oblique to Poupart's ligament. (From Halsted, W. S.: Johns Hopkins Hosp. Bull. 14: 208, 1903. Figure V.)

Both Halsted operations for hernia (1889 and 1903) involved deliberate abolition of the normal obliquity of the inguinal canal. His first technique brought the cord structures to a subcutaneous level at a point near the anterior superior spine of the ilium; the second brought the cord through the abdominal wall near the pubic spine.

The original Halsted operation for inguinal hernia should be abandoned by all, at it was by Halsted himself, because hernias tend to recur at the site of exit of the cord. The later Halsted operation has little to recommend its use except perhaps in conjunction with operations for undescended testis.

In Halsted's last paper, prepared on Aug. 26, 1922, just 12 days prior to his death, speaking of the different aspects of the various details of his method, he says that he had abandoned the reduction of the size of the cord by excising

part of the veins, because it gave rise to hydrocele. Then speaking of the ultimate results and relative importance of the many variations for the repair of inguinal hernia, he says: "Indeed I have not seen a single paper since Bassini's which contributed anything new."[3]

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SPLENOHEPATIC ARTERIAL ANASTOMOSIS FOR ANEURYSM OF HEPATIC ARTERY

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ANEURYSMS of the hepatic artery and its terminal branches are rather rare lesions and most of the patients have died of complications. In approximately one-half of the reported cases, the artery of origin was the hepatic artery proper, in one-third the right hepatic, in one-tenth the left hepatic artery and, in the remaining few, it was a combination of right and left branches, the cystic or an accessory hepatic artery.[13]

Sheridan[34] stated that Wilson, in 1809, reported the case of a 50-year-old man who died of hemorrhage from rupture of an intrahepatic aneurysm the size and shape of a heart; this seems to have been the first case to be reported.

The purpose of this paper is to review the more recent literature on hepatic artery aneurysms and to report the successful treatment of two aneurysms of the hepatic artery proper. The first, extending from its origin to near its bifurcation, was treated by excision of the aneurysm and restoration of arterial blood flow to the liver by means of an end-to-end splenohepatic arterial anastomosis. This form of treatment has previously been suggested.[15, 16, 34] The second, extending from its origin to the origin of its gastroduodenal branch, was treated by excision of the aneurysm and construction of the medial wall of the vessel joining the gastroduodenal and hepatic arteries, by means of a 6-0 silk arterial suture (after the method of Hansbrough and Lipin[16]).

DIAGNOSIS OF HEPATIC ARTERY ANEURYSM

Previous authors agree that the preoperative diagnosis of hepatic artery aneurysm has been infrequently made. The first symptoms are often those caused by massive intra-abdominal hemorrhage. Various authors have reported the triad of upper abdominal pain, hemorrhage, and jaundice. Less common are fever, headaches, constipation, ascites, a bruit heard over the abdominal wall, and a pulsating abdominal tumor.[29] The duration of symptoms has varied from a few minutes to several months. The site of rupture with consequent hemorrhage may be intraperitoneal (in one-half of cases) or into the duodenum, gall bladder, or portal vein.[12, 13, 18, 22, 33, 35, 36, 38] There have been reports of simultaneous ruptures in two sites. Melena and sometimes hematemesis follow when the hemorrhage is into the biliary or gastrointestinal tract.

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A shadow may be found on x-ray examination of the abdomen owing to calcification of the walls of an aneurysm of the arteriosclerotic type.[21, 23] Kirklin[27] reported demonstration of an aneurysm by means of a transthoracic aortogram. Aneurysms of the hepatic artery have been discovered and recognized during the course of an abdominal operation for some other condition.[16] Hepatic artery aneurysms may produce a filling defect of the duodenum and a narrowed duodenal cap demonstrable by means of a barium meal x-ray examination.[7]

THE NATURAL HISTORY OF HEPATIC ARTERY ANEURYSM

Hepatic artery aneurysms develop the same complications as aneurysms of other arteries within the abdomen. Oddly enough, hepatic aneurysms following upper abdominal operations are extremely rare.[31]

In general, hepatic artery aneurysms rupture sooner or later[11, 13, 37] and need not attain a large size before this serious and often fatal complication occurs.[10] Approximately 80 per cent of patients with this lesion first seek help at the time of rupture and hemorrhage.[13]

Dwight and Ratcliffe[10] reviewed the literature on hepatic aneurysm and found, in 89 cases recorded by 1952, that three-quarters were extrahepatic, one-quarter intrahepatic, and, in three cases, both types were present. Barnett and Wagner[3] reviewed cases of hepatic artery aneurysm causing obscure abdominal hemorrhage and found that the average time of survival in 15 cases, from onset of pain until death, was 25 hours, with a range from 10 minutes to 8 days. The lesions varied in length from 1 to 6 cm. (average, 3.3 cm.) and in diameter from 0.25 to 4.5 cm. (average, 2.5 cm.). Most of the true aneurysms have been of small size while the larger ones have been of the false type.[29, 31]

In their review, Dwight and Ratcliffe found that 33 patients had had severe systemic infection such as pneumonia, empyema, or typhoid fever, 18 patients arteriosclerosis, 7 syphilis, 6 cholelithiasis, and 7 had had trauma in the region of the liver. A detailed history was available in 74 of the reported cases. The duration of symptoms varied from a few hours to as long as 2 years; in some cases collapse from massive hemorrhage had been the first sign of the presence of an aneurysm. In 52 of these 74 cases there had been pain, in 38 jaundice had been evident, in 43 gastrointestinal hemorrhage, and in 24 cases the patients had had pain, jaundice, and gastrointestinal hemorrhage. Barnett and Wagner[3] found that the sex incidence was fairly evenly distributed, although aneurysms were more common in males, and that the average age of the patients was 38.4 years, with a range from 18 to 62 years.

Sheridan[34] found that 99 cases of hepatic artery aneurysm had been reported before July, 1955. Two patients had been cured and 90 had died. The majority of the reports were of autopsy cases in which the lesion was not suspected before death. Thirty-four patients had been operated upon, but in many cases the diagnosis was not made at operation.

REVIEW OF TREATMENT

The prognosis is very poor for patients with hepatic artery aneurysms. Very few such patients can be expected to survive for extended periods of time

because spontaneous cure by thrombosis must occur only very rarely. Successful surgical treatment has been carried out in a few cases. In 111 cases of hepatic artery aneurysm, reviewed by Hansbrough and Lipin[16] in February, 1959, only 12 patients had survived direct surgical approach. They reported their case in which cure was obtained by excision of the aneurysm proximal to its gastroduodenal and right gastric branches. In this case the collateral arterial blood supply, which was preserved, was adequate to maintain the liver. In August, 1959, Browning, Clauss, and MacFee[6] reported that 123 cases of hepatic aneurysm were recorded in the literature and they added 2 cases of their own.

The following is a list of successful methods of treatment and the names of the authors involved:

SUCCESSFUL CASES OF SURGICAL TREATMENT

Ligation of hepatic artery	
Houdard[21]	1954
Kading[25]	1919
Kehr[26]	1903
Colmers[9]	1921
Quattlebaum[33]	1954
Spector[35]	1957
Mainetti[28]	1956
Excision and ligation of hepatic artery or main branch	
Browning, Clauss, and MacFee[6]	1959
Inui and Ferguson[22]	1956
Kirklin, Shocket, Comfort, and Huizenga[27]	1955
Hejnal[17]	1957
Suture of aneurysm to liver	
Anderson[1]	1919
Wiring of aneurysm	
Dwight and Ratcliffe[10]	1952
Wiring of aneurysm and suture of arteriovenous aneurysm	
Wheeler[39]	1957
Endoaneurysmorrhaphy	
Hess, W.[19]	1953
Sheridan[34]	1956
Giuseffi and Collins[12]	1954
Excision and repair of hepatic artery	
Paul[32]	1951
Reactive plastic wrapping	
Steelquist (two)[36]	1955
Excision with preservation of collateral arterial supply to liver	
Hansbrough and Lipin[16]	1959

This review of the literature on treatment of aneurysms of the hepatic artery and its two main branches reveals that success has been achieved in 21 cases prior to the two reported in this paper.

CASE REPORTS

CASE 1.—Mr. W. D., aged 59 years, was referred to one of us (J. R. McC.) for surgical treatment of chronic cholecystitis and cholelithiasis by Dr. S. R. Cooper. He had had symptoms of gall bladder disease for 5 years. In addition to marked fatty food intolerance, he had had intermittent attacks of epigastric and right upper quadrant abdominal pain. He had not had either jaundice or melena. On Dec. 19, 1958, he had had an extremely severe attack of epigastric pain that radiated to the right subcostal region and into the back, associated with much nausea and abdominal distention, lasting for a period of several days. After this severe attack there were several mild attacks of right upper quadrant abdominal pain in the interval preceding his admission to the Royal Victoria Hospital on

March 10, 1959. Prior to admission a cholecystogram had revealed the presence of gallstones in a functioning gall bladder and a chest film had shown some dilatation and tortuosity of the thoracic aorta.

On admission his blood pressure was 180/105 mm. Hg, the pulse rate was 88 per minute; the hemoglobin value was 80 per cent, and urinalysis revealed no abnormality. History and physical examination revealed no other significant information.

The patient was taken to the operating room on March 11, and laparotomy was performed. Abdominal exploration revealed the gall bladder to be chronically diseased: It contained stones, its wall was scarred, and there were many acquired adhesions about it. The common bile duct and head of the pancreas were normal. There was an aneurysm of the hepatic artery, measuring about 8 by 6 by 4 cm., lying just superior and posterior to the body and head of the pancreas and between the first part of the duodenum and the liver. The mass had an expansile pulsation with each heartbeat and an obvious thrill could be felt through its wall. The aneurysm could be partially emptied of blood by digital compression and the lumen seemed to be partially filled with thrombus. The proximal end of the aneurysm involved the origin of the hepatic artery from the celiac axis. The distal portion of the hepatic artery, just before its bifurcation into right and left hepatic branches, was pulsatile and appeared to be normal beyond the distal end of the aneurysm (Fig. 1). Cholecystectomy and appendectomy were carried out but treatment of the aneurysm was deferred. The postoperative course was very satisfactory. Further examination revealed a systolic bruit in the right subcostal region over the aneurysm.

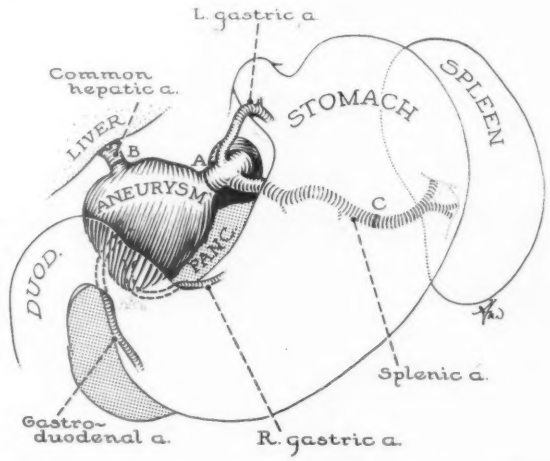

Fig. 1.—Line drawing of findings at operation in Case 1. (Explanation in text.)

The patient was taken to the operating room on March 25, 1959, for treatment of the hepatic artery aneurysm which was expected to prove fatal within a short period of time if not removed. The aneurysm had not changed in size or shape in the interval between March 11 and March 25, but postoperative adhesions made the dissection difficult. Both the gastroduodenal and right gastric arteries were involved in the wall of the aneurysm and, therefore, were of no functional use.

The wall of the aneurysm was very thin in its inferior portion and during the dissection it was seen to have almost reached the point of rupture. Old thrombus material began to extrude from it and it was necessary to repair a defect in the wall with sutures to facilitate further dissection. Pott's clamps were placed on the hepatic artery at its origin (near *A* in Fig. 1), and at its point of division into right and left branches (near *B* in Fig. 1). The intervening aneurysm was then excised. The stump of the hepatic artery was closed with sutures flush with the wall of the celiac axis.

The splenic artery was then dissected free for a distance of 7 or 8 cm., divided (at *C* in Fig. 1), and its splenic end ligated. The proximal free portion of the splenic artery was

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swung over to the right for end-to-end anastomosis to the hepatic end of the hepatic artery. It was necessary to remove thrombus from the lumen of the hepatic artery at point *B* (Fig. 1), in order to restore complete patency and a free backflow of blood from the liver. End-to-end splenohepatic anastomosis was then established with 6-0 black silk arterial suture (Fig. 2). Prior to completing this anastomosis the splenic artery was filled with dilute heparin solution. After removal of the Pott's clamps, excellent pulsations could be palpated and observed in the splenic artery, in the short segment of hepatic artery and in the right and left hepatic arteries, proving patency and free flow of arterial blood to the liver. The spleen was not removed. The hepatic arterial blood supply to the liver was occluded for a period of 40 minutes during the dissection.

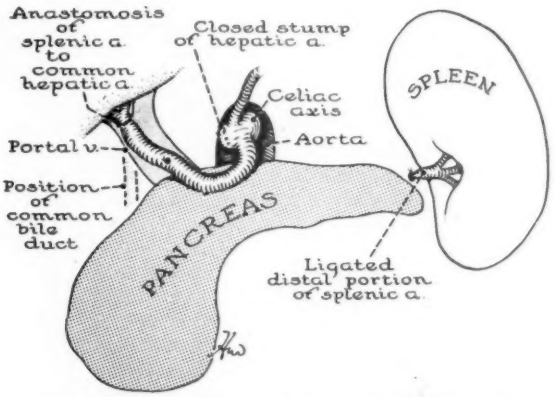

Fig. 2.—Line drawing to show the splenohepatic arterial anastomosis in Case 1.

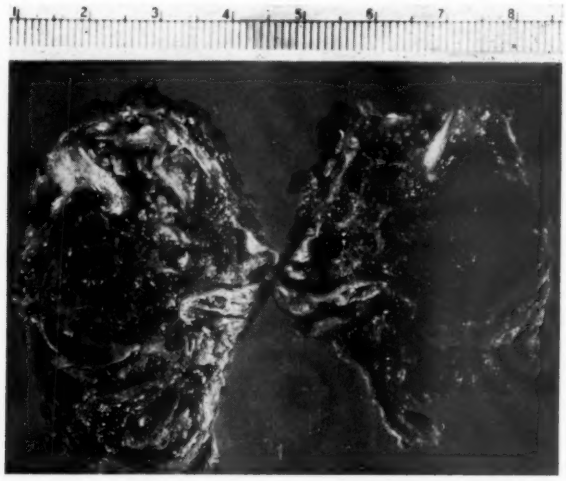

Fig. 3.—Photograph of longitudinal section of excised hepatic artery aneurysm in Case 1, with the anterior portion turned over to the left to expose its inner aspect. See Fig. 4.

The postoperative course was uneventful and the postoperative liver function tests all remained within normal limits. The patient was discharged in excellent condition on April 4.

Examination of the specimen revealed the aneurysm of the hepatic artery to be arteriosclerotic and that it had previously ruptured on its inferior aspect to form an additional false aneurysm (Figs. 3 and 4). Microscopic examination confirmed these findings.

Upon consideration of the history it seemed probable that the arteriosclerotic aneurysm had ruptured on Dec. 19, 1958, at the time of the patient's very severe attack of pain

(previously thought to have been due to gall bladder disease), forming the false aneurysm with the very thin wall and intraluminal thrombus.

The patient has remained in good health since the operation and has returned to work in his executive position. A faint bruit is audible over the anterior abdominal wall anterior to the site of the splenohepatic anastomosis. This, in addition to his excellent state of health, was taken as further proof that the splenohepatic arterial anastomosis has remained patent and functioning. Dr. Stubington, of the Department of Cardiology, was kind enough to make a phonocardiographic tracing of this bruit and it is reproduced in Fig. 5.

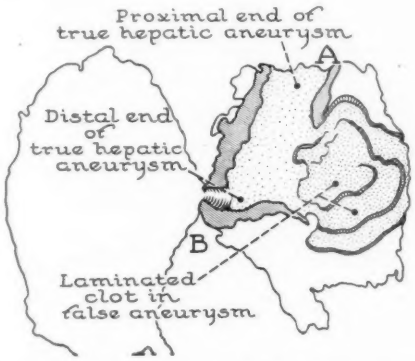

Fig. 4.—Outline sketch of specimen shown in Fig. 3, to show more clearly the true and false components of the aneurysm in Case 1.

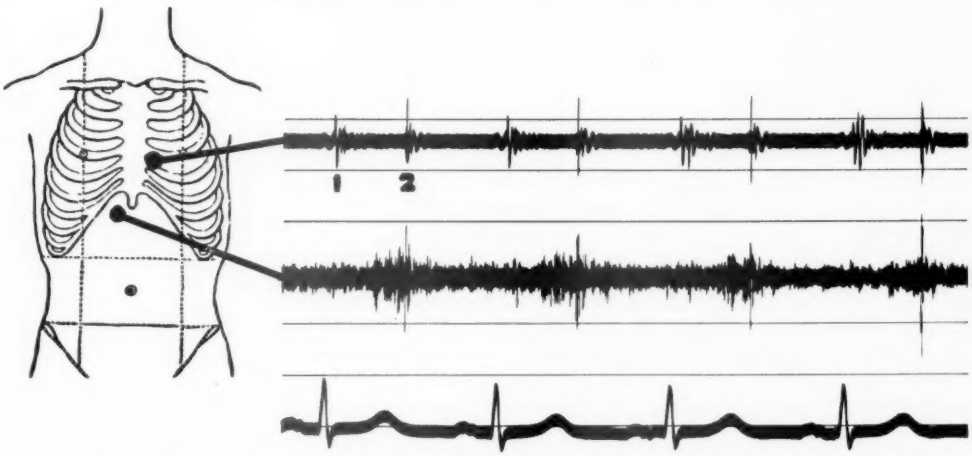

Fig. 5.—*Upper strip:* Phonocardiographic tracing from fourth left intercostal space showing normal heart sounds 1 and 2. *Second strip:* Sound tracing from right subcostal site showing a continuous murmur with middle and late systolic accentuation. The second heart sound is transmitted to this area. *Lower strip:* Electrocardiogram. (These three tracings were made simultaneously in Case 1.)

CASE 2.—Mr. M. H., aged 54 years, was seen in consultation on Aug. 23, 1959, because of the development of signs and symptoms of an acute abdominal condition. He had been in the hospital since July 17, 1959, when he had been admitted after sustaining multiple injuries when struck by an automobile. The injuries had included lacerations and abrasions of the head, trunk, and extremities, fracture of the right humerus, fracture of tarsal bones of the right foot, and fracture of 7 ribs on the right side, from the sixth to the twelfth. There had been a contusion of the right lung with x-ray evidence of pleural effusion, and a right perirenal hematoma. There had been no evidence of intra-abdominal visceral injury.

When seen by one of us (J. R. McC.) on August 23, he was in severe pain, localized in the right upper abdominal quadrant, the pulse rate was 100 per minute, the blood pressure stable at 140/90 mm. Hg, and a large tender mass was present below the right costal margin.

There was evidence of fluid in the right pleural space and no signs of ventilation of the lower and middle lobes of the right lung. Auscultation over the abdomen disclosed the presence of a systolic bruit or murmur in the right upper quadrant over the site of the palpable mass. Bowel sounds were diminished, rectal examination was negative. The temperature was 101° F., having been elevated each day for the last 3 days. X-ray films of the chest and abdomen revealed an opacity in the right lower pulmonary region but nothing of significance in the abdomen. The femoral pulses were normal.

The patient was observed for 2 hours. During this time the pulse rate rose from 100 to 120 per minute, the abdominal pain became agonizing and the abdominal mass became more tender and larger, and the abdominal muscular rigidity increased. The systolic abdominal bruit became less distinct. He was then taken to the operating room for laparotomy with a presumptive diagnosis of acute cholecystitis and aneurysm of an intra-abdominal artery, possibly traumatic and possibly complicated by hemorrhage.

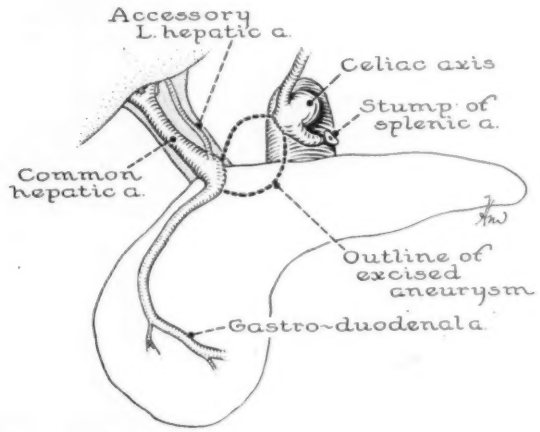

Fig. 6.—Line drawing to indicate the site of the aneurysm and the anatomic features after its removal in Case 2.

The abdomen was opened through a right paramedian incision. The mass proved to be due to a distended, gangrenous gall bladder surrounded by adherent omentum and transverse colon. There was no free fluid or blood in the peritoneal cavity. The gall bladder was removed; the common bile duct was normal. The source of the bruit heard before the operation was searched for and a thrill was palpable to the left of the bile duct. Further exposure and dissection revealed an aneurysm of the hepatic artery proper, measuring 2.5 by 1.5 cm., extending from its origin from the celiac axis to its gastroduodenal branch. The hepatic artery distal to this point was normal. Exploration of the entire abdominal cavity and viscera revealed no other lesion; the appendix had been previously removed.

The splenic artery was carefully dissected to obtain a free proximal segment 6 cm. in length. To one's dismay it was found to be greatly narrowed by arteriosclerosis to an internal diameter of only 2 mm. so that it was ligated and abandoned as unsuitable for splenohepatic anastomosis.

Further dissection of the aneurysm was then carried out. Occlusion of the aneurysm did not obliterate the distal hepatic artery pulse, but simultaneous occlusion of the gastroduodenal artery near its origin did, and the distal hepatic artery then collapsed and became flaccid. This was interpreted as proof that the gastroduodenal artery was an adequate source of collateral arterial blood supply to the liver. The aneurysm was excised and the defect in the celiac axis repaired by suture. The arterial wall defect caused by division of the hepatic artery at the point of origin of the gastroduodenal artery was closed by means of a 6-0 arterial silk suture (after the method of Hansbrough and Lipin[16]) (Fig. 6). The result was a single vessel composed of gastroduodenal and common hepatic artery. Excellent arterial pulsations were visible and palpable in the hepatic artery and its right and left

branches at the end of the procedure. The abdominal wound was closed and the patient made an uneventful recovery from the laparotomy. No bruit is now audible.

The pathologists reported arteriosclerotic changes in the wall of the excised aneurysm of the hepatic artery.

DISCUSSION

A review of the literature concerning aneurysm of the hepatic artery and its terminal branches, the right and left hepatic arteries, reveals that complications are the same as those of other aneurysms. These complications are always serious and usually fatal. Rupture of the aneurysm with serious or fatal intra-abdominal hemorrhage is the most common complication, whereas pressure effects upon adjacent structures are less common.

Preoperative diagnosis of aneurysms of the hepatic artery has seldom been made and, even during laparotomy performed for serious hemorrhage, the diagnosis has often been missed and the cause of the bleeding found later, during postmortem examination. In other instances, the hemorrhage has not been controllable and, in still others, it has been intrahepatic and not accessible for surgical control.

Several different methods of surgical treatment have been tried and, in the 21 successful cases recorded prior to those reported in this paper, most success has attended ligation of the hepatic artery, with or without excision of the aneurysm.

It has been shown that ligation or excision of the celiac axis, or ligation of the hepatic artery proximal to its preserved gastroduodenal artery rarely, if ever, leads to fatal liver necrosis.[2, 5, 31] On the other hand, ligation of the hepatic artery distal to the gastroduodenal and right gastric branches usually results in death from liver necrosis or failure.[4, 8, 20, 30] Several authors have described collateral arterial supplies to the liver but the collateral supply in any given instance is unpredictable and often inadequate after ligation or excision of the hepatic artery near the liver beyond its larger branches.[14, 24] In fact, death may ensue after ligation of either the right or left hepatic artery alone. If the hepatic artery has been occluded by the aneurysm it means that the collateral circulation is adequate and has been functioning for some time, so that the aneurysm may be excised and the hepatic artery ligated proximal and distal to it without jeopardizing the nutrition of the liver.

It would seem obvious that the surgical procedure to carry out in an effort to cure a patient with a hepatic artery aneurysm would have to be chosen at the time of the operation in accordance with the circumstances encountered. The main objectives of treatment are two: (a) to remove the threat of a serious complication, such as massive hemorrhage owing to rupture of the aneurysm, and (b) to preserve an adequate arterial blood supply to the liver and so protect it from functional failure or actual necrosis.

The possibility of rupture of an aneurysm of the hepatic artery should always be borne in mind when dealing with obscure intra-abdominal hemorrhage because this will permit more accurate diagnosis and the application of curative surgical techniques in a greater proportion of cases.

Although restoration of arterial blood flow to the liver after excision of an aneurysm of the hepatic artery has been suggested by previous authors,[15, 16, 3] it has generally been considered unlikely to be successful. In the first case herein reported, excision of the aneurysm was necessary to prevent imminent rupture of the aneurysm with probable fatal hemorrhage. Because the aneurysm involved all branches of the hepatic artery likely to carry an adequate collateral circulation, it was necessary to bring a new source of arterial blood to the distal end of the hepatic artery just proximal to its bifurcation. The splenic artery proved to be suitable for this purpose and an end-to-end splenohepatic anastomosis was successful. It is realized that this technique has its anatomic and technical limitations and that it is probably applicable only to extrahepatic aneurysms involving the hepatic artery proper. However, it has proved successful in the case reported and it is recommended on both theoretical and practical grounds when circumstances permit. In the second case, it was possible to construct the artery, after excision of the aneurysm, in such a way as to preserve an excellent collateral arterial circulation to the liver.

SUMMARY

Much of the literature pertinent to the problem of hepatic artery aneurysm has been reviewed with emphasis upon successful methods of treatment.

The case of a 59-year-old man with an arteriosclerotic aneurysm of the hepatic artery proper, complicated by the development of a secondary false aneurysm, is reported. The aneurysm was completely excised and the hepatic arterial blood supply was restored by means of a splenohepatic arterial anastomosis. A second case, that of a 54-year-old man with an arteriosclerotic aneurysm of the hepatic artery proper, is also reported. In this instance the aneurysm was excised and the arterial blood flow to the liver maintained by preserving the connection between the gastroduodenal branch and the common hepatic artery distal to the aneurysm. These would appear to be the twenty-second and twenty-third surgical cures of aneurysm of the hepatic artery, and the first successful splenohepatic arterial anastomosis to be reported.

ADDENDUM

Since this paper was accepted for publication a third case of aneurysm of the hepatic artery has been encountered.

CASE 3.—The patient, Mrs. C. D., aged 28 years, was admitted to the Surgical Service of the Royal Victoria Hospital on Nov. 20, 1959. She complained of right upper quadrant abdominal pain of severe degree, present for approximately 18 hours. She had had pain in the same region, for a period of one day, one week prior to admission. Examination revealed marked tenderness with rebound pain in the right upper quadrant of her abdomen and a distended, tense gall bladder was palpable 2 fingerbreadths below the right costal margin. Her temperature was 99.6° F., pulse rate 84 per minute, blood pressure 110/70 mm. Hg, and the hemoglobin level was 14.6 Gm. per cent. The serum amylase level was normal (50 units), the urinalysis was negative, and x-ray examination of the chest and abdomen revealed no abnormalities.

The diagnosis of acute obstructive cholecystitis was made and the patient was taken to the operating room at 7:30 P.M. on November 20. A right upper paramedian abdominal

incision was made, using general anesthesia, and the gall bladder was found to be acutely inflamed and distended with inflammatory adhesions between it and the greater omentum. A gallstone was palpable in Hartmann's pouch. The cystic duct and common bile duct were of normal size and no stones were palpable within them. Exploration of the remainder of the abdomen revealed no other lesion until attention was again directed toward the region of the bile duct and the cystic artery was isolated. The cystic artery was large and lay inferior to the cystic duct. Further palpation of the cystic artery revealed the presence of a pronounced systolic thrill. Dissection was extended and the thrill was found to originate in the hepatic artery, which was dilated in a fusiform manner to an outside diameter of 1.0 cm. over a length of 2 cm. (Fig. 7).

The cholecystectomy was completed and then the regional arterial tree was dissected free to expose the celiac axis, the proximal portions of the splenic and left gastric arteries, the hepatic artery and its terminal branches, the right and left hepatic arteries. The gastroduodenal artery, cystic artery, and a smaller artery to the common bile duct all originated from the right hepatic artery; the right gastric artery originated from the left hepatic artery (Fig. 7).

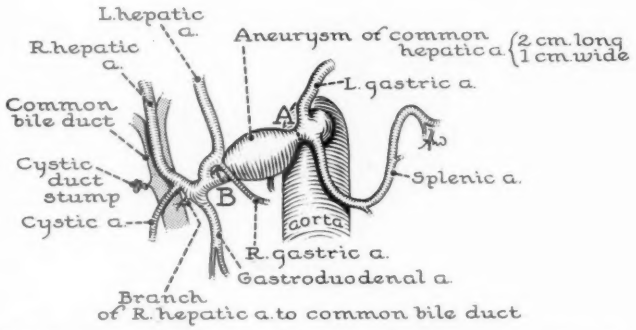

Fig. 7.—Line drawing of findings at operation in Case 3.

Spring artery clamps were temporarily applied in various places and in this way the adequacy of collateral circulation to the liver, with occlusion of the hepatic artery proper, was demonstrated.

The following courses of action seemed possible: (1) to dissect free a segment of the splenic artery and establish a splenohepatic arterial anastomosis after excision of the aneurysm; (2) to leave the fusiform aneurysm in situ and prevent its further enlargement by supporting its wall with a Teflon arterial prosthesis sutured about it; or (3) to excise the aneurysm and depend upon the collateral circulation, via the gastroduodenal, right gastric, and other arterial branches distal to the aneurysm, which seemed adequate. This last form of treatment was chosen as the best.

Clamps were placed upon the hepatic artery distal and proximal to the aneurysm and the aneurysm was completely excised. The proximal stump was closed by means of a 4-0 arterial silk suture at its origin from the celiac axis (Fig. 7, *A*). The distal stump was closed by a similar suture at its bifurcation (Fig. 7, *B*). The right and left hepatic arteries continued to pulsate well and only a very faint thrill was palpable.

The postoperative course was complicated by temporary atelectasis of the posterior basilar segment of the right lower pulmonary lobe; this promptly cleared with appropriate therapy. The patient was discharged from the hospital in good condition on Dec. 5, 1959.

The pathologist reported subacute cholecystitis and cholelithiasis. The hepatic artery aneurysm specimen, after fixation in formalin, measured 1.5 cm. in length and it had an inside diameter of 5 mm. Its wall was thin on one side. The luminal surface appeared to be smooth. The wall of the aneurysm showed focal areas which were pale in staining, and these areas also showed fibrillation of elastic fibers.

The patient was found to be quite well and completing a normal convalescence 5 weeks after the operation.

ACKNOWLEDGMENT

We wish to thank Dr. H. F. Moseley, the Surgeon in Charge in Case 3, for his great courtesy in requesting one of us (J. R. McC.) to carry out the treatment of the hepatic artery aneurysm in this case.

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ARTERIAL CANNULATION FOR EXTRACORPOREAL CIRCULATION UTILIZING THE EXTERNAL OR COMMON ILIAC ARTERY

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A NUMBER of sites for arterial cannulation preparatory to whole body perfusion have been utilized, ranging from the ascending aorta itself to the femoral artery. In their original description of the median sternotomy incision for intracardiac operations with whole body perfusion, Julian and associates[3] advocated use of the ascending aorta, as had Dodrill and co-workers.[1] Use of the subclavian artery was satisfactory when exposure was obtained by means of bilateral anterior thoracotomy. However, the emergence of the median sternotomy incision[3, 4] as the one of choice for most intracardiac operations forced abandonment of the use of this vessel for such purposes.

Utilization of one or both femoral arteries has gained wide acceptance, although the relatively small size of this rather peripheral vessel has been something of a disadvantage in our experience. In infants and small children especially, the femoral artery is so small as virtually to preclude the insertion of a large cannula or catheter.

The right iliac artery has been found to serve admirably in patients of all sizes.* The external iliac artery is usually employed. However, when upon exploration this vessel appears to be too small, the common iliac artery may be readily reached for cannulation through the same incision.

Since the resistance to flow offered by a cannula is proportional directly to its length and inversely to the fourth power of its radius, preference always has been for a cannula of the largest possible internal diameter and the shortest practical length. These ends have been met most satisfactorily through the use of a short, thin-walled, metal cannula, highly polished internally. A set of such cannulas adapted for use in the iliac artery is pictured (Fig. 1).

The advantages of a short cannula of large lumen are apparent in view of the small pressure gradients encountered at various flows with cannulas of this type.[2]

TECHNIQUE

The right iliac artery is exposed extraperitoneally through a transverse incision placed low in the right lower quadrant of the abdomen. The anterior rectus sheath is incised over the lateral half of the muscle, the incision being carried about 1 cm. lateral to the edge of the rectus muscle. The external iliac

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*Dr. John C. Callaghan, Edmonton, Alberta, suggested this technique to us.

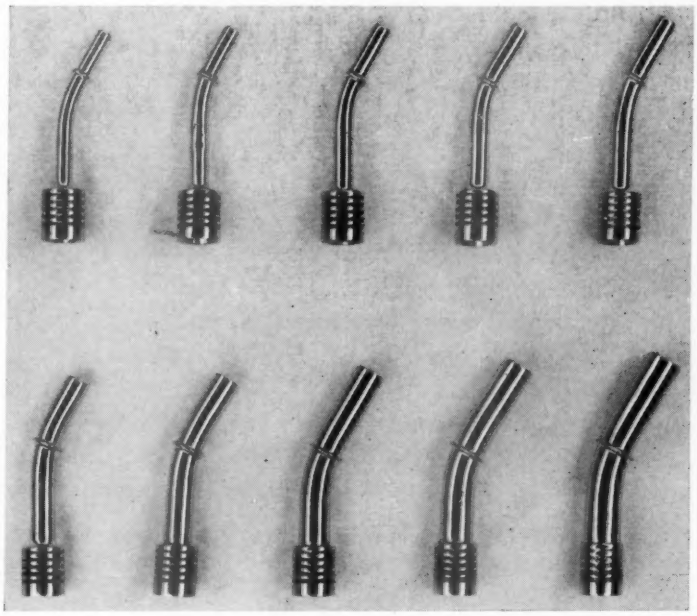

Fig. 1.—Stainless steel arterial cannulas for use in the iliac artery in establishing extracorporeal circulation. The internal diameter in millimeters is inscribed on the proximal part of the shaft. Sizes range from 2.4 to 5.9 mm. (This complete set is available through V. Mueller & Company, Rochester, Minnesota.)

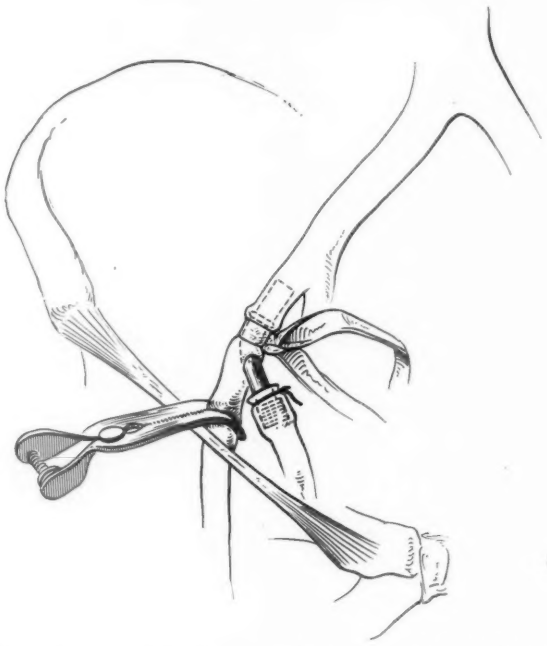

Fig. 2.—Cannulation of the external iliac artery completed and ready for extracorporeal circulation. The special cannula is retained in place with an umbilical tape tightened behind the flange of the cannula shaft.

artery is easily visualized after dissecting down to it in the extraperitoneal plane. An umbilical tape is passed around the vessel, which is then freed from the surrounding connective tissue. A fine-toothed Potts clamp is placed proximally and a bulldog clamp is used distally. The artery is incised transversely through about two-thirds of its circumference. A small curved clamp is introduced proximally into the lumen, and the artery is stretched gently to accommodate the largest possible cannula. The cannula is retained in the vessel by tightening the umbilical tape behind the flange of the cannula shaft (Fig. 2). After decannulation, the vessel is repaired by means of a continuous everting mattress stitch. This repair is facilitated if the adventitia has been stripped previously from the site of the arteriotomy.

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SELECTIVE VISCERAL ARTERIOGRAPHY

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A SIGNIFICANT incidence of partial occlusion of the major visceral branches of the aorta has recently been demonstrated in elderly subjects.[6] Using translumbar aortography to detect such occlusion has proved impractical because of the following disadvantages: (1) superimposition of vascular structures of several organs due to the patient's prone position; (2) uneven filling of a vessel with contrast medium, due to improper needle position or other causes; (3) danger of an intramural injection, which may be caused by a slight shifting of the needle tip after it has been correctly placed; (4) difficulty of aortic puncture in some patients with rotoscoliosis; and (5) difficulty in producing selective arteriography by puncture of a selected vessel. Selective arteriography would require less contrast medium, and better visualization would result from the heavier concentration of the medium in a single vessel. Also, serious complications are possible with the translumbar approach, such as the dissection of the aortic wall by contrast medium.

There has, therefore, been great interest recently in other approaches to abdominal aortography.[1, 3, 5, 8] In 1940, Castellanos and Pereiras[4] outlined retrograde or counter-current aortography. They published an x-ray reproduction made by this technique of an infant in the lateral projection, showing contrast medium in the lower thoracic and abdominal aorta with good filling of the visceral branches. Farinas,[7] in 1941, described his modification of Castellanos' technique: the insertion of a catheter into the abdominal aorta through a trochar in the femoral artery. He pointed out that this technique would permit selective arteriography. He did not, however, employ the curved catheter which is necessary to cannulate a selected vessel successfully, nor did he employ fluoroscopy to control the tip of the catheter.

Bierman and associates,[2] in 1951, reported the selective catheterization of branches of the abdominal aorta with a fixed curved-tip catheter manipulated under fluoroscopy. Under general anesthesia, the catheter was introduced through an exposed carotid or brachial artery and threaded into the aorta. Bleeding was controlled by pressure from soft rubber bands. Even though Bierman's patients suffered from other serious diseases, his reports of a high incidence of complications discouraged other investigators from using this technique.

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In 1953, Seldinger[11] described a modification in which a needle was introduced into the femoral artery percutaneously. A catheter guide was inserted through the needle, which was then removed. Under fluoroscopic control, the radiopaque polyethylene catheter was introduced over the guide into the proper position. The leader was then withdrawn. The chief advantages of this system are that a large catheter may be introduced and the artery is not directly exposed.

Tillander,[12] in 1953, described a catheter tip with a gold-plated, iron ball-and-socket joint. An external magnetic field was used to modify the curve of this catheter tip so that it might be easily introduced into selected vessels. The need for heavy equipment has prevented the widespread use of this method.

Our contribution to the technique of the femoral artery approach to abdominal aortography is a modification of the Lehmann catheter: a catheter tip which may be straight or curved. It is kept straight during its passage through the artery to the level of the diaphragm, since here a straight catheter is less likely to dislodge or disturb arteriosclerotic plaques. The catheter is then curved for cannulation of the selected vessel. Such a catheter is produced by being heated in a curved mold so that its distal 4 to 7 cm. describes an arch of 90 to 120 degrees. A thin, flexible, stainless steel stylet is then introduced to straighten the tip of the catheter. Upon removal of the stylet, the catheter reassumes the molded curve.

Before using this catheter with patients, the technique was developed in 7 experimental animals in which constriction of the artery had been produced. Constriction was successfully demonstrated in all 7 cases (Fig. 1).

TECHNIQUE

Patients considered for selective study of the celiac axis, the superior mesenteric artery, or either renal artery were carefully examined. All who demonstrated significant arterial insufficiency of the lower extremity were eliminated. After local anesthesia was administered, the femoral artery was exposed. A 4 to 6 cm. incision of the skin proved adequate in most instances, but the length of the incision must vary with the thickness of the fat layer in this area. An effort was made to preserve all branches of the femoral artery and vein. After its exposure, the femoral artery was carefully palpated for evidence of arteriosclerotic involvement. If such evidence was found, the procedure was terminated at this point. Umbilical tape was used around the femoral artery and its branches, since any type of clamp might tear the intima or damage the vessel and contribute toward thrombosis. By twisting umbilical tape around the femoral artery with the catheter in place, adequate control of bleeding could usually be secured (Fig. 2). After the umbilical tape was applied, a weak heparin solution was injected distal to the point of occlusion.

Before the catheter was introduced into the femoral artery, it was carefully checked for patency and for proper curvature after removal of the stylet. A thin coating of sterile mineral oil was a helpful lubricant during the manipulation required to position the catheter and to slide it along the femoral artery.

The catheter was never forced during its passage from the iliac arteries into the aorta. If it did not advance easily, it was withdrawn 2 to 3 cm., rotated, and gently advanced again. Using this method, we failed only once to introduce the catheter into the upper aorta.

Fluoroscopy was begun after the catheter had advanced above the level of the diaphragm. For visualization of the celiac axis or the superior mesenteric artery, the patient was rotated to a lateral position. The renal arteries were best visualized with the patient in the supine position. The radiopaque catheter tip permitted the fluoroscopist to guide the catheter to within several millimeters of the desired orifice. It is possible that the injection of 4 to 5 c.c. of 70 per cent radiopaque medium may facilitate location of the catheter, but this has not been our experience.

Fig. 1.

With the catheter properly positioned, 10 to 12 c.c. of 70 per cent contrast medium was rapidly injected, and multiple films were made. These films were developed rapidly, so that, if necessary, another injection could be given without the catheter remaining in the aorta for a prolonged period of time.

As the catheter was withdrawn from the femoral artery, continuous suction by a syringe was applied to assure the removal of small clots that may have formed around the catheter tip. To repair the artery, 5-0 arterial silk was used.

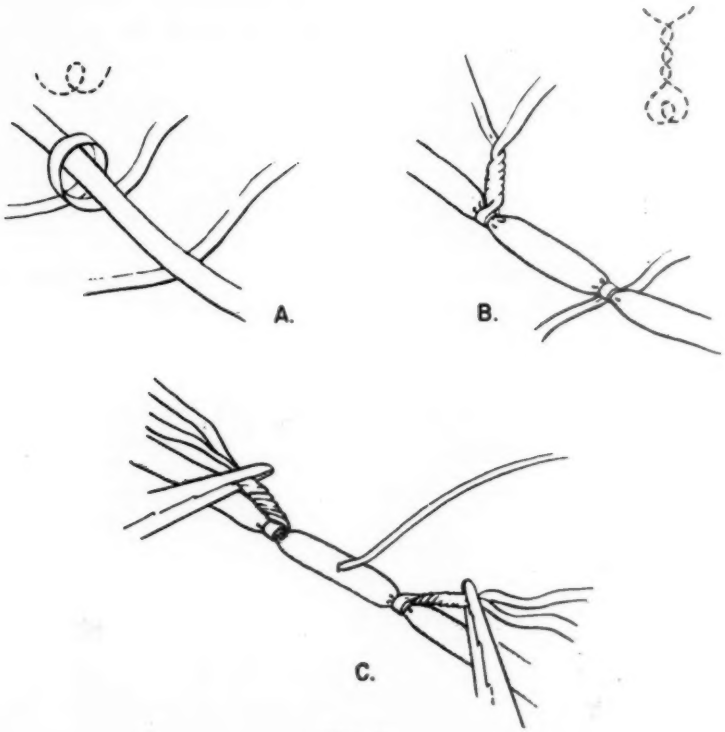

Fig. 2.

Fig. 3.—Irregularity of renal artery and the difference in the density of the dye in the area of irregularity. Patient had malignant hypertension.

We have used this technique in 22 instances, and there have been only two complications. A 52-year-old patient with malignant hypertension later developed a subcutaneous hematoma at the site of artery repair. A small wedge of the femoral artery was removed, and the artery resutured. The severe hypertension of this patient may have contributed toward this complication. One case of thrombosis also occurred. Embolectomy was performed about 15 hours after the procedure. The patient's recovery was uneventful.

DISCUSSION

Because of our limited experience with this technique, few conclusions can be drawn at this time. We have revealed constriction of the celiac axis once, of both the celiac axis and the superior mesenteric artery once, and of the renal arteries three times. We have also shown one renal arteriovenous fistula and one patent ductus arteriosus. In two or three instances there has been a suggested constriction, but our limited experience did not permit specific conclusions concerning these patients. Marked constrictions seem easily demonstrated, but the detection of slight degrees of constriction will probably require a broader experience in interpreting the film (Fig. 3).

Any method of diagnosis is good only if the benefits of the data obtained far outweigh the risks involved. Good judgment in selecting patients, and caution in executing the procedure must be exercised.

SUMMARY

A technique for selective visceral arteriography is described. Criteria for the selection of patients, the procedure, and experience with this procedure in the experimental laboratory and in patients are presented.

To date no serious complications have arisen in patients studied by this technique. Adequate visualization of constricted areas of one or more branches of the abdominal aorta was obtained in 5 patients.

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POSTOPERATIVE RECURRENCE OF BREAST CANCER AFTER THIRTY-TWO YEARS

A Case Report and Review of the Literature

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CANCER of the breast and malignant melanoma rank first among the neoplasms that are known to have a high rate of late recurrence. Cases of extremely late recurrence have always been found to be of special interest for three reasons: (1) they demonstrate that the term, "cure," in cancer therapy must be used with reservation; (2) they point out the necessity for a life-long follow-up of treated and supposedly cured cancer patients; and (3) they influence all theoretical reflections on cancer development and growth.

The following case of breast cancer in which the tumor recurred locally 32 years after a radical mastectomy was seen and followed at the Evanston Hospital.

CASE REPORT

Mrs. M. S. had a left radical mastectomy performed at the age of 41 because of a scirrhous carcinoma of the left breast in December, 1921, in St. Elizabeth Hospital, Lafayette, Indiana. The patient received postoperative radiation therapy. Detailed records of these initial therapeutic procedures have not been kept. In March, 1925, a nodule was excised from her right breast at the Evanston Hospital Association which was histologically diagnosed as chronic mastitis.

On Jan. 27, 1954, the patient was again admited to the Evanston Hospital Association, this time for a 3 cm. subcutaneous nodule which had developed on her left anterior chest wall, approximately 3 cm. medial to the old mastectomy scar. The patient had first noticed it one month prior to admission. It was very firm and seemingly fixed to the fifth and sixth ribs in the left parasternal region. On Jan. 28, 1954, the lesion was excised by sharp dissection by Dr. John L. Savage.

The microscopic histologic report read: "Groups and cords of cells infiltrate dense connective tissue. These cells form no particular recognizable structure. An occasional glandlike space appears to be artifactual and intercellular bridges cannot be demonstrated. Mitotic figures are frequent. Diagnosis: Undifferentiated carcinoma in chest wall."

A postoperative course of x-ray treatments was given tangentially to an area 8 by 10 cm. on the left anterior chest wall including the recent excision wound. A total of 4,200 r was delivered to a depth of 4 cm. within 28 days.

A careful physical examination of the patient at that time as well as at regular intervals since the operation in January, 1954, failed to reveal any evidence of remnant tumor or of a new primary cancer. The patient was last seen in January, 1959, and was enjoying excellent health.

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COMMENT

The reported case has stimulated us to review the literature for similar accounts on extremely late recurrence of breast cancer. As early as 1876, Boeckel[4] reported a 29-year recurrence. In 1887, two cases were published in the English literature.[6, 29] Before the turn of the century two more cases appeared in the French literature. Both were recurrences after 30 years.[15, 31] Since then 50 more case reports have appeared in the American and European literature.

In view of the rarity of recurrences after 15 or more years, it is surprising that Bohlig[5] was able to present 4 cases of his own, Hartmann[14] 6 cases, and Gordon-Taylor[12] 7 cases. Except for one of Bohlig's cases, which he describes well, all three authors published no detailed information on their cases.

The only larger collection of late recurrences of breast cancer is the one by Morton and Morton,[22] published in 1953. Their table includes recurrences after the tenth year as well as cases of breast cancer with repeated recurrences which were treated by multiple excisions over periods longer than 10 years. In the case of Daland,[9] 22 operations were done within 24 years. These chronic carcinomas are of much interest. However, they should not be confused with cases of late recurrence. There are 33 cases of breast cancer listed in Morton's table that recurred 15 or more years after operation.

We have collected a total of 55 cases with recurrence of the breast cancer after more than 15 years. They are listed in Table I in the order of the duration of their cancer-free interval. The table also contains brief information on the name of the author, the year in which the case was first reported, site of recurrence, whether or not a histologic examination of the primary or secondary lesion was performed, which breast was affected if not both, the histologic type of the carcinoma, whether or not postoperative radiation treatment was given, and if an autopsy was performed. Where this information is missing on the table, it has not been given in the original report. If, as in 3 cases, the original report was not available, this has been stated.

It is not intended to discuss all cases individually, but we may focus briefly on the 3 reports that claim the longest cancer-free intervals before the recurrence manifested itself. The longest period was reported in 1932 by Chauffard.[7] He describes that "several red-violet nodules, doubtlessly cancer," appeared in the mastectomy scar 50 years after the operation. The patient died of pneumonia several months later. No mention is made of histologic examinations or of autopsy findings.

A local recurrence after 46 years was reported by Hartmann[14] in 1942. He gives no details.

Davidson and Ratcliffe[10] published a detailed case report in 1946 of a woman who had a bilateral mastectomy for cancer of both breasts 40 years prior to the appearance of cancerous lymph node involvement at the base of the neck. The patient died after 3 years. On autopsy, there was no evidence of a new primary cancer. Histologically, the metastatic tumor was compatible with breast carcinoma.

TABLE I. REPORTED CASES OF CARCINOMA OF THE FEMALE BREAST WHICH RECURRED FIFTEEN OR MORE YEARS AFTER OPERATION

NUMBER	RECURRENCE (YEARS)	AUTHOR	DATE OF PUBLICATION	SITE OF RECURRENCE	PERFORMED HISTOLOGIC EXAMINATION (PRIMARY/SECONDARY)	REMARKS
1	50	Chauffard[7]	1932	Mastectomy scar	?	
2	46	Hartmann[14]	1942	Mastectomy scar	?	No details reported
3	40	Davidson and Ratcliff[10]	1946	Base of neck, left	+/+	Carcinoma both breasts; autopsy
4	34	Daland[9]	1945	Mastectomy scar	?	
5	32	Danckers et al.	1958	Subcutaneous parasternal	?/+	Scirrhus left breast; postoperative irradiation
6	32	Lewis and Rienhoff[19]	1932	Liver	?	Operation by Halstedt; no detail reported
7	31	Bohlig[5]	1955	Brain	?	Right breast; autopsy
8	31	Bowlby	?	?	?	Cited by Gordon-Taylor[12]
9	31	Steward	1925	?	?	Cited by Gordon-Taylor[12]
10	30	Gordon-Taylor[12]	1939	Pelvis	?/+	Operated upon by Wallace
11	30	Heurtaux[15]	1899	Mastectomy scar	?	Cited by Perry, publication not available
12	30	Verneuil[31]	1888	Mastectomy scar	+/+	Scirrhus
13	29	Boeckel[4]	1870	?	?	Cited by Labhardt, publication not available
14	29	Morton and Morton[22]	1953	Skin of axilla	?/+	Left breast; first recurrence after 12 years
15	27	Perry[24]	1948	Pleura, mediastinum	−/+	Left breast; autopsy
16	25	Bade[3]	1946	Lymph nodes neck, bilateral	?	
17	25	Bryant[6]	1887	Mastectomy scar	?	Thought to be new primary
18	25	Matas	?	Mastectomy scar	?	Letter to Ransohoff[27]
19	23	Gordon-Taylor[12]	1939	Mastectomy scar	?	No details reported
20	23	Potherat[25]	1909	Presternal skin	+/+	Carcinoma both breasts, 6 months apart
21	22	Bade[3]	1946	Skin parasternal, left	?	Left breast
22	22	Gordon-Taylor[12]	1939	Mastectomy scar	?	No details reported
23	22	Richard[28]	1942	Left humerus	?/+	Left breast; postoperative irradiation
24	21	Gordon-Taylor[12]	1939	Mastectomy scar	?	No details reported
25	21	Haagensen[13]	1956	Pleura, lung	+/+	Right breast, autopsy
26	21	Monod[21]	1942	Axilla same side	+/+	No details reported
27, 28, 29	20	Bohlig[5]	1955	?	?	3 cases; no details reported

30	20	Ransohoff[27]	1907	?	?	Personal information from Deaver to R.
31	20	Ficarra[11]	1952	Generalized	?/+	Adenocarcinoma both breasts; autopsy
32	20	Haagensen[13]	1956	Left supraclavicular	+/+	Left breast
33	20	Lewis and Rienhoff[19]	1932	Mastectomy scar	?	No details reported
34	20	Mitchell[20]	1952	Mastectomy scar	+/+	Adenocarcinoma left breast
35	20	Ransohoff[27]	1907	Mastectomy scar	+/+	Scirrhus right breast[27]
36	19	Bull	?	Generalized	?	Cited by Ransohoff[27]
37	19	Hartmann[14]	1942	Vertebrae	?	No details reported
38	19	Hartmann[14]	1942	Mediastinum	?	No details reported
39	19	Josephy[17]	1951	Left axillary lymph node	?/+	Right breast; autopsy
40	19	Smith[29]	1887	Excision scar	+/–	Right breast
41	17	Coley	?	?	?	Cited by Ransohoff[27]
42, 42a	17	Gordon-Taylor[12]	1939	Mastectomy scar	?	2 cases; no details reported
43	17	Powers[26]	1910	Mastectomy scar	+/+	Scirrhus left breast
44	17	Wawro[32]	1954	Subcutaneous parasternal	+/+	Thought to be new primary
45	16	Arnsperger[2]	1905	Mastectomy scar	?	Right breast
46	16	Gordon-Taylor[12]	1939	Mastectomy scar	?	No details reported
47	16	Hartmann[14]	1942	Sternum	?	No details reported
48	16	Hartmann[14]	1942	Ovary	?	No details reported
49	16	Morton and Morton[22]	1953	Right axilla, skin of right shoulder	+/+	Right breast; postoperative irradiation (500 r)
50	16	Nunn[23]	1899	Mastectomy scar	?	
51	16	Uffreduzzi[30]	1930	?	+/+	Cited by Chilko and Quastler[8] publication not available
52	15	Chilko and Quastler[8]	1945	Mediastinum, pleura	+/+	Medullary carcinoma left breast; autopsy
53	15	Huguenin and Gillet[16]	1938	Mastectomy scar	+/+	Scirrhus right breast; postoperative irradiation
54	15	Hartmann[14]	1942	Lung	?	No detail reported

We have reviewed the original publications whenever possible. As could be expected, the degree of accuracy used by the different authors in their case reports varies greatly, ranging from a mere mention of the case to the most detailed description of the case history, physical findings, and its histopathology. We have included also the poorly reported cases, though their scientific value is debatable. All cases in Table I have in common the fact that those who reported them were, at least through clinical evidence, convinced of the presence of a true recurrence.

The recurrent breast cancer, even if histologically shown to be adenocarcinoma, can theoretically be simulated by two other conditions: (1) a new primary breast cancer originating from mammary tissue that was left behind at the time of the original operation, and (2) a metastasis from a second primary carcinoma hidden in the opposite breast or in any other part of the body. One will usually succeed in satisfactorily ruling out a metastatic lesion originating from a second primary by means of a thorough clinical work-up of the patient, histologic comparison of the original and the new lesion, and a continued observation of the patient and eventual autopsy. However, it is often difficult or impossible to conclusively demonstrate that one is not dealing with a new primary breast cancer that has developed from remnant mammary tissue at the site of the original operation. This point has recently been emphasized by Wawro.[32] In 1954, this author published a paper entitled, "The Case for de novo Origin of Late Recurrence of Cancer of the Female Breast," in which he presented a subcutaneous parasternal recurrence which had developed 17 years after radical mastectomy for a comedocarcinoma. A block dissection of the recurrence had been performed and histologic examination showed "fibrocarcinoma." There also was residual breast tissue demonstrated in the skin flap. On the basis of the histologic reports, Wawro suspected new primary carcinoma. This is not necessarily correct. In some intraductal carcinomas break-through occurs and a typical infiltrating lesion develops,[1] which may be especially true after an operation that has failed to remove all malignant tissue and has possibly carried malignant cells into the interstices. We have included Wawro's case in our table, being aware of the possibility that we are dealing with a new primary lesion. This possibility exists for all other reported recurrences to the same degree but may be a small factor if a good radical mastectomy procedure was performed.

As is shown in Table II of 55 collected recurrences of breast cancer, 21 had developed directly in the mastectomy scar, 5 in the skin or subcutaneous tissues in the immediate neighborhood of the scar, and 6 in the regional lymph nodes. Fourteen were distant metastases; their distribution is also shown. In 9 cases, the exact location of the recurrence was not stated.

Of the 14 cases with distant metastases as the first recurrence, only 5 are reported to have had an autopsy by which a second primary cancer as the source of the metastatic lesion was ruled out. In the remaining 9, no mention of a postmortem examination was made. How in these cases the diagnosis of a true recurrence was established reliably remains questionable. The total number of autopsies performed in all 55 cases is only seven.

TABLE II. SITE OF FIRST RECURRENCE IN 55 LATE RECURRENT BREAST CARCINOMAS

Mastectomy scar		21
Skin near mastectomy scar		5
Regional lymph nodes		6
Distant metastases		14
Pleura and lung	3	
Bone	4	
Mediastinum	1	
Brain	1	
Liver	1	
Ovary	1	
Generalized	3	
Not reported		9
Total		55

Postoperative irradiation following the operation of the original lesion was reported in 4 cases of the 55. One of these, however, received only 500 r, an amount that appears too small to be of value in the treatment of malignant disease. Many of the patients were operated upon at a time when routine postoperative irradiation for breast cancer was not yet practiced.

Histologic examination of both the original cancer and the recurrence was reported in 14 cases. Twice the original lesion alone was stated to have been histologically examined and six times the recurrence alone. Thirty-three case reports failed to mention any histologic examination.

It is occasionally stated in the literature that scirrhous carcinomas form the largest percentage of the carcinomas with late recurrences. In this group with 55 case reports, the primary lesion was histologically classified only seven times. It was called a scirrhous in 5 cases and comedo and medullary carcinoma in one case each. Although these are too few for any definite conclusions, they tend to support the clinical impression that the majority of late recurrences are made up of scirrhous lesions.

SUMMARY

1. A case history of carcinoma of the female breast is presented in which a local recurrence developed 32 years after the radical mastectomy.

2. The American and European literature has been reviewed for similar cases. A total of 55 reports on breast carcinomas which recurred 15 or more years after the operation was collected, evaluated, and tabulated.

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A CLINICAL EVALUATION OF d-PANTOTHENYL ALCOHOL

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OVER the years surgeons have had a vital interest in any agent which could safely stimulate parasympathetic activity in postoperative patients. The agent most commonly used at present is neostigmine in various concentrations. The potent parasympathomimetic action of this drug is presumably the result of inhibition of cholinesterase at the neuromyal junction, allowing the acetyl and choline groups to join readily.[2] This action is considered to be unphysiologic by some and because of this, as well as the fact that unhappy clinical experience can result from the use of neostigmine, the substance, d-pantothenyl alcohol,* has recently been introduced. This substance is a derivative of the optically active dextro isomer of the complex organic substance, pantothenic acid.

In 1951 Lipmann won the Nobel Prize for his isolation of co-enzyme A. It was found at this time that 11 per cent of the co-enzyme A molecule was composed of pantothenic acid.[5] It is recognized that co-enzyme A is necessary for the reaction of acetate and choline to form acetylcholine, and that this product is the transmitter substance at the autonomic ganglion and postganglionic parasympathetic nerve endings. It has been theorized that stress situations such as surgery lower the acetylcholine reservoir in the gastrointestinal tract which leads to a condition of parasympathetic embarrassment. Further inferential reasoning is that, if d-pantothenyl alcohol were present, co-enzyme A would be more readily available for the acetylation of choline with the resultant resumption of bowel activity.

Many species of animals have been placed on a pantothenic acid–deficient diet with no constant pattern being observed.[2] However, no metabolic role for pantothenic acid other than that of being a part of co-enzyme A has been described.[8] There is also no known syndrome of pantothenic acid deficiency in man. An experiment using human subjects[1] consisted of such a small number (4) of subjects that no conclusions can be drawn from it.

Since there is a need for more clinical information regarding this product as recently noted by Stone and associates,[7] the Third (Boston University) Surgical Service at the Boston City Hospital undertook a study to determine whether the use of d-pantothenyl alcohol is efficacious in postoperative patients. One hundred patients were selected at random from the general surgical service; 50 received d-pantothenyl alcohol and 50 were used as controls (Table I).

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*Ilopan supplied by the Warren-Teed Company, Columbus, Ohio.

TABLE I. SUMMARY OF TYPES OF SURGICAL CASES USED IN STUDY

OPERATION	d-PANTOTHENYL ALCOHOL	CONTROL
1. Cholecystectomy	9	10
2. Subtotal gastrectomy	5	5
3. Bowel resection	8	11
4. Hemorrhoidectomy	2	3
5. Herniorrhaphy	11	6
6. Exploratory laparotomy	2	4
7. Gynecologic surgery	3	6
8. Appendectomy	7	4
9. Gastroenterostomy	2	0
10. Perforated ulcer	1	1
Totals	50	50

d-Pantothenyl alcohol was given in a dosage schedule of 2 c.c. (500 mg.) intramuscularly immediately after surgery in the recovery room. This dose was repeated in 2 hours and in 12 hours. We did not feel that these injections should persist over several days, since postoperative ileus is a self-limiting situation. If a drug were given over several days, it would be impossible to determine whether the return of parasympathetic activity was spontaneous or drug induced.

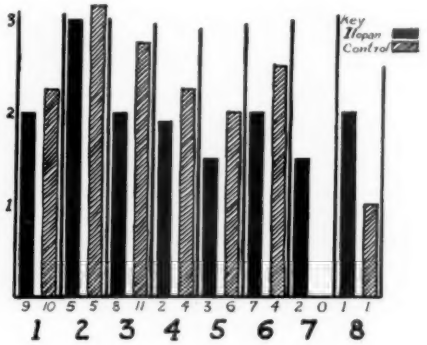

Fig. 1.—Number of days for evacuation of flatus. Numbers on abscissa: (1) cholecystectomy, (2) subtotal gastrectomy, (3) bowel resection, (4) laparotomy, (5) gynecologic procedures, (6) appendectomy, (7) gastroenterostomy, and (8) perforated ulcer. The small numbers are patients in each group. Ordinate represents days.

Among the results d-pantothenyl alcohol has been credited with achieving is an increase in the rapidity of resumption of bowel function postoperatively. This phenomenon was evaluated by studying the onset of peristaltic sounds, postoperative evacuation of flatus, and defecation. On occasions bowel sounds were audible on the day of surgery only to disappear the following day. Elimination of feces depended on efficiency of preoperative enemas as well as the speed with which a patient returned to a regular diet; consequently we felt that the best criterion of bowel reactivity was the passage of flatus. We realized that this is a highly subjective end point. The patients were impressed, however, with the vague idea that the length of their hospital stay was highly dependent upon the knowledge of when they were first cognizant of passing flatus. It was therefore usual for the examiners to obtain accurate information.

As can be seen from Fig. 1, patients receiving d-pantothenyl alcohol passed flatus about one-half day earlier than those in the control group. It is our feeling, however, that this finding did not improve the patients' general postoperative convalescence.

Forty-eight patients were placed on Levin tube suction postoperatively. Those who had bowel resections and received d-pantothenyl alcohol had an earlier resumption of bowel activity which resulted in their suction tubes being removed on an average of one day earlier. Other patients necessitating nasogastric suction showed on an average no decrease in the duration of their need for decompression (Fig. 2).

Alleged also to be a function of d-pantothenyl alcohol has been a reduction in the incidence of postoperative urinary retention. Eight (16 per cent) of the experimental group and 10 (20 per cent) of the control group had preoperative indwelling catheters and were eliminated from the tabulation. In the control group, 7 (17.5 per cent) needed catheterization and in the experimental group 9 were catheterized. A patient in this latter series, however, had a urinary volume of only 150 c.c. and was eliminated leaving 8 patients (19 per cent) who had urinary retention while receiving d-pantothenyl alcohol (Fig. 3).

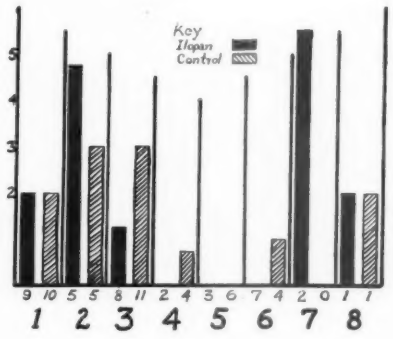

Fig. 2.

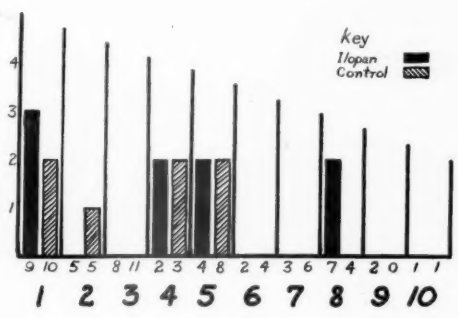

Fig. 3.

Fig. 2.—Number of days on suction. Abscissa same as Fig. 1. Ordinate shows days on suction.

Fig. 3.—Number of patients catheterized. Numbers on abscissa: (1) cholecystectomy, (2) subtotal gastrectomy, (3) bowel resection, (4) hemorrhoidectomy, (5) herniorrhaphy, (6) laparotomy, (7) gynecologic procedures, (8) appendectomy, (9) gastroenterostomy, and (10) perforated ulcer. The small numbers are patients in each group. Ordinate represents number of patients catheterized.

Postoperative distention associated with paralytic ileus is not frequently seen on our surgical service since with the earliest indication prophylactic decompressive maneuvers are immediately instituted. During this study there were but 2 patients (4 per cent) in each group who developed distention, and for the reason mentioned previously never presented any serious or prolonged problem.

In the experimental group 8 (16 per cent) required enemas as opposed to 4 (8 per cent) of the control group. Obviously no significance can be attributed to these figures except that in this study d-pantothenyl alcohol did not decrease a patient's statistical chance of receiving an enema.

CONCLUSIONS

1. d-Pantothenyl alcohol did accelerate slightly the return of bowel activity postoperatively but this did not facilitate postoperative convalescence or earlier discharge from the hospital.

2. d-Pantothenyl alcohol did decrease the necessary time on nasogastric suction only in those patients undergoing bowel resections.

3. d-Pantothenyl alcohol did not influence the incidence of postoperative distention, urinary retention, or lessen the number of postoperative enemas.

SUMMARY

This study was undertaken to evaluate postoperative benefits one might gain from the use of d-pantothenyl alcohol in those patients undergoing abdominal, inguinal, and rectal surgery. When this preparation was given there was a slightly earlier onset of bowel activity, but this did not enhance the patients course or earlier discharge from the hospital. It is, therefore, felt from the foregoing results that clinical benefits are not achieved from the use of d-pantothenyl alcohol to justify its routine postoperative use.

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Pediatric Surgery

CONDUCTED BY MARK M. RAVITCH, M.D.

UNIVERSAL AGANGLIONOSIS OF THE COLON

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A DANISH pediatrician, Hirschsprung, delivered a lecture in Berlin in 1886 based on the postmortem examination of 2 of his patients, both baby boys, who died at the ages of 7 and 11 months, respectively. These infants had suffered symptoms of chronic constipation, abdominal distention, and intermittent episodes of intestinal obstruction. The necropsy report contained the following observation: "When the abdomen was opened, two enormously dilated loops of large intestine presented themselves . . . the sigmoid and the even more severely distended transverse colon. Also, the other parts of the large intestine appeared somewhat dilated: only the rectum was not enlarged, but seemed to be the site of some kind of slight narrowing."

Unfortunately, no significance was attached to the latter part of Hirschsprung's observation and for the next 6 decades attention was focused on the dilated rather than the constricted large bowel. Investigation during the past 60 years has gradually erased the erroneous original concept of the etiology of congenital megacolon. Today it is generally agreed that the narrow, spastic, aganglionic portion of the distal colon is responsible for the development of the dilated proximal colon which is characteristic of Hirschsprung's disease.

A logical method for the surgical treatment of Hirschsprung's disease was described by Swenson in 1948.[24] Since that time, Swenson[22] has performed over 200 operations utilizing the abdominoperineal pull-through procedure for congenital megacolon. Swenson and others have recently reported on the success of this pull-through procedure.

It was not until 1955 that Swenson and Fisher[25] reported the involvement of the entire colon by Hirschsprung's disease in 2 of their first 150 cases. The literature contains many reports concerning the treatment of congenital megacolon, but few reports have been published in which the aganglionic defect has involved the entire colon. Howard and McBurney[11] collected 8 cases and added another case. We have collected 26 cases and wish to report a case of surgical correction of aganglionosis affecting the entire colon.

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CASE REPORT

Baby S. B., a first child, was born on Feb. 12, 1955. She was a full-term baby delivered by cesarean section because of cephalopelvic disproportion. The birth weight was 3,150 grams. During her neonatal hospitalization, the infant was noted to have some difficulty in passing meconium, and required frequent rectal examinations to initiate bowel movements. Roentgenograms revealed distended loops of small intestine with multiple fluid levels, and the colon was not definitely identified (Figs. 1 and 2). Stools were passed with the assistance of rectal irrigations and the baby was discharged home on the eighth day.

Fig. 1. Fig. 2.

Figs. 1 and 2.—Erect and frontal inverted films. There are considerably distended loops of small bowel distributed throughout the abdomen. Fluid levels are present. Colon is not definitely identified. Appearance suggests presence of obstruction in distal small bowel.

She was readmitted at 5½ weeks of age with the history of having passed 2 soft yellow stools daily from the time of her discharge until 2 weeks prior to readmission. Since that time, the baby had become constipated and bowel movements occurred only after the use of suppositories. Changes of formula failed to relieve the constipation. By March 24, 1955, the baby was noted to be acutely ill with vomiting and abdominal distention. Roentgenograms revealed many loops of dilated small intestine and a transverse loop colostomy was performed. She did well for 4 days, passing spontaneous bowel movements via the colostomy. On the fifth postoperative day, a small evisceration was noted at the lateral

angle of the right upper quadrant transverse incision. This was reduced and repaired. The postoperative course was complicated by diarrhea. She was discharged on June 22, 1955.

On Oct. 19, 1955, she was readmitted because of dysfunction of the colostomy. A fecal impaction was relieved by saline colostomy irrigations and the patient was discharged. Another fecal impaction was similarly treated in November, 1955.

She was readmitted in December, 1955. A barium enema performed at this time is shown in Fig. 3. At laparotomy on Dec. 14, 1955, a biopsy obtained from the sigmoid colon revealed the absence of ganglion cells. Multiple biopsies were then obtained back to the site of the transverse colostomy. There were no ganglion cells found in any of the specimens. The distal transverse, descending, and sigmoid colon was then excised. The patient's postoperative course was essentially benign and she was discharged on Dec. 28, 1955.

She was readmitted for relief of fecal impactions in January and again in June of 1956. On Dec. 13, 1956, she was readmitted and the bowel was prepared with saline enemas and neomycin. At operation on December 19, a biopsy was taken from the ascending colon. A small and reduced number of ganglion cells were seen on frozen section. A biopsy was then obtained from the ileum approximately one foot from the ileocecal junction. Normal ganglion cells were seen on frozen section. The small intestine was transected at this point. The distal ileum, cecum, ascending colon, and proximal transverse colon with the colostomy were resected. The distal sigmoid and rectum were then resected and an ileo-proctostomy was performed using the standard Swenson pull-through technique.

Fig. 3.—Barium enema performed 7 months after establishment of a transverse colostomy. The large defect in the mid-descending colon is a fecalith.

The infant's postoperative course was complicated by perianal ulcerations due to the numerous liquid bowel movements during the first 2 weeks of her convalescence. These lesions responded to local treatment and regulation of her diet.

At the time of her hospital discharge she weighed 17 pounds. In the next 2½ years her weight gradually increased to 30 pounds. Her appetite was good and her bowel movements usually were solid or semi-solid and averaged two to three per day.

On June 15, 1959, she was readmitted to the hospital with a history of intermittent generalized abdominal pains for 2 weeks and a 5-day history of nausea with occasional

periods of vomiting, anorexia, and increasing lethargy. Associated with these symptoms were abdominal distention and a decrease in the urinary output.

Physical examination revealed: blood pressure 100/60 mm. Hg, pulse 140 regular and strong, respirations 20, temperature 100° F. She appeared as a thin, lethargic, dehydrated Negro girl. She was 4 years 4 months of age and weighed 27 pounds. Pertinent findings included a slightly distended abdomen. The bowel sounds were hyperactive with occasional borborygmi. There was no tenderness. The liver, spleen, and kidneys were not enlarged. A well-healed left rectus scar was present. Rectal examination revealed a competent sphincter with a markedly distended terminal ileum. When the finger was removed there followed profuse flatus and yellowish-brown foul-smelling watery stool.

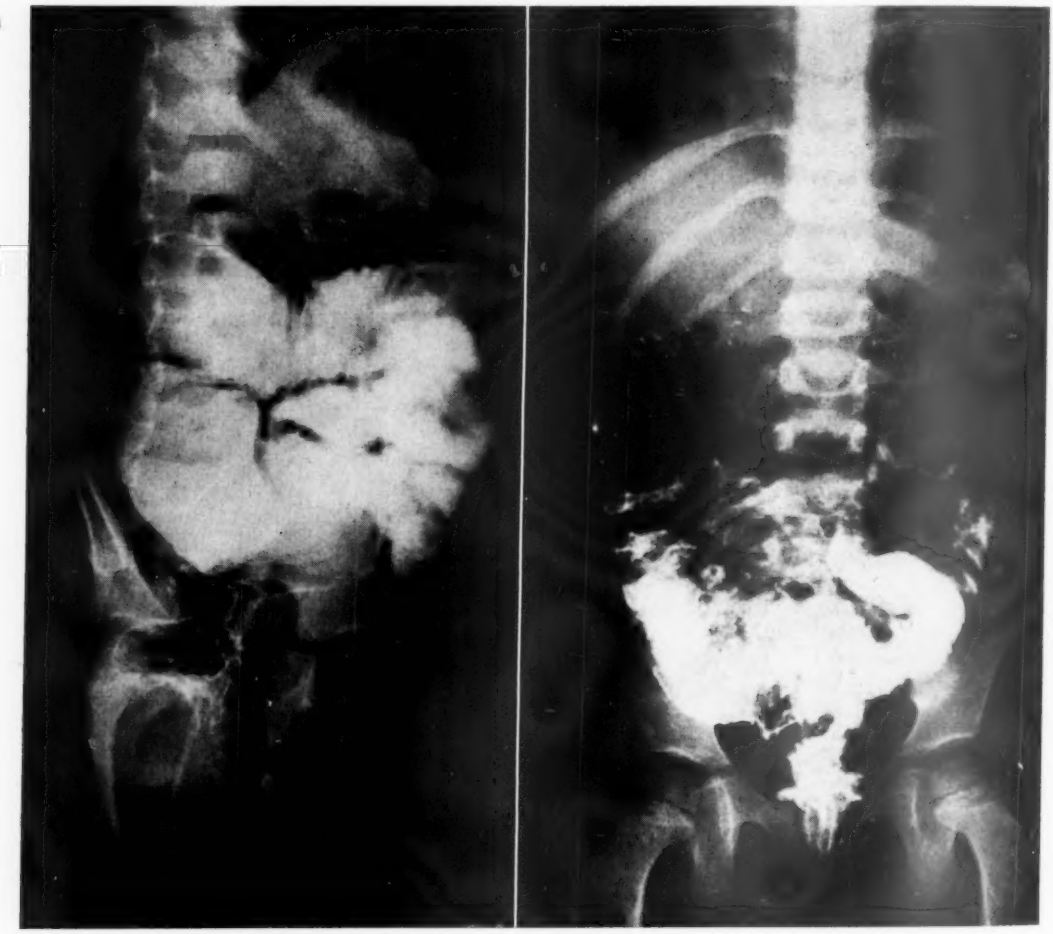

Fig. 4. Fig. 5.

Figs. 4 and 5.—Barium enema performed on patient's last admission. There is marked dilatation of the ileum which has the appearance of being colonized.

The admitting hemogram was: hemoglobin 9.0 Gm. per cent, white blood count 13,800 with 68 per cent polymorphonucleocytes and a shift to the left (11-57-0). The urinalysis was normal. The blood urea nitrogen was 44. Electrolytes were sodium 141, chloride 70, and potassium 7.5. The following day after the patient had received intensive intravenous therapy, the electrolytes were sodium 149, chloride 104, potassium 5.9, carbon dioxide 23.0, and the blood urea nitrogen was 11.

A barium enema (Figs. 4 and 5) and obstructive series revealed markedly distended loops of ileum with multiple fluid levels down to the level of the ileoproctostomy. There was no free air under the leaves of the diaphragms.

Proctoscopy was performed to a level of 4 inches. There were noted to be 4 discrete areas of ulcerations with exudation in the terminal ileum with the mucosa appearing congested. The site of the anastomosis was confirmed by rectal examination and there was no constriction. The level of the anastomosis was 5 cm. from the anal verge.

During the next three days the hemoglobin gradually dropped to 7.2 Gm. per cent and on June 19 she received 250 c.c. whole blood transfusion. The hemoglobin rose to 10.3 Gm. per cent. Her first 3 days of hospitalization were marked by temperature spikes to 103° F. On admission she was started on oral erythromycin and neomycin with the tentative diagnosis of enterocolitis. Repeat stool cultures were negative for pathogens.

Follow-up obstructive series performed on June 20 showed no change from the admitting roentgenograms. That evening the patient was noted to have a large greenish-brown bowel movement. Her respirations became labored and she died despite all resuscitative measures. Permission for a postmortem examination was refused.

First Operation: Description of Surgical Specimen.—

Gross: The specimen consisted of 3 separate segments of large bowel including sigmoid, descending, and part of transverse colon. The combined length of the 3 segments measured 15.5 cm., and the average circumference 2.5 cm. The serosal and mucosal layers were normal, and there was no definite hypertrophy of the muscle coats. Multiple longitudinal sections of the entire length of the specimen were embedded in paraffin and stained with hematoxylin and eosin for histologic examinations.

Microscopic: There was some hypertrophy of the inner circular coat of the muscularis propria and hyperplasia of the lymph follicles in the mucosa. The mucosa was well preserved. The submucosa contained dense collagenous tissue with many small blood vessels and multiple small nonmyelinated nerves, usually lying close to the vessels. No ganglion cells were found. The myenteric plexus also was devoid of ganglion cells, but there were a good many small nerves between the two muscle coats. This picture was fairly uniform in all the sections except for some variation in the number and size of the nerves at different levels. No ganglion cells were found at the proximal site of resection.

Second Operation: Description of Surgical Specimen.—

Gross: The specimen which was received in three parts, consisted of rectosigmoid, right colon, and terminal ileum and cecum. The segment of rectosigmoid was 10 cm. long and 2 cm. in greatest diameter. The right colon contained the stoma of a colostomy at its distal end. This segment of bowel was 10 cm. long and markedly dilated, measuring 10 cm. in its circumference at the proximal end of resection. There was hypertrophy of the muscle coats. The mucosa was intact. The resected segment of terminal ileum was 36 cm. long and the attached cecum 8 cm. These too were dilated and thickened, the ileum having a circumference of 6.5 cm., the cecum 10 cm. Except for a slight granularity, the serosa was unremarkable. The mucosa showed no evidence of inflammation or ulceration. Multiple longitudinal sections were taken through all 3 segments of bowel. These were embedded in paraffin and stained with hematoxylin and eosin.

Microscopic: Sections through the rectosigmoid revealed a thin wall without muscle hypertrophy, and moderate thickening of the submucosa. No ganglion cells were found in the submucous and myenteric plexus. Nerves were seen primarily between the two muscle coats. The distal segment of the right colon, including the colostomy site, was devoid of ganglion cells. However, considerable hypertrophy of the muscle coats was present. The first rare ganglion cells were encountered in the proximal portion of the ascending colon, some in submucous location, some in the muscle coats. But this was not a continuous plexus as in a normal bowel.

In the hypertrophied and dilated cecum, ganglia gradually became more abundant and larger, especially in the myenteric plexus. No definite abnormality of the autonomic plexus was found in the terminal ileum which, however, presented considerable hypertrophy and a mild chronic inflammatory infiltration of the mucosa.

In summary, there was a total aganglionosis of the large intestine with the exception of the cecum where a gradual transition to a normal ganglionic pattern took place.

DISCUSSION

Table I summarizes the cases of Hirschsprung's disease collected from the literature in which the aganglionic involvement had affected the entire colon, or

TABLE I

AUTHOR	NUMBER OF CASES	SEX	ROENTGENOGRAMS	INVOLVEMENT	OPERATION	RESULT
Swenson	2	M	Normal barium enema; scout film showed generalized distention of small bowel loops	Entire colon	1. Loop ileostomy; right colectomy 2. Left colectomy 4 months later 3. Ileoproctostomy 2 weeks later	Alive
		M	Right colon dilated on barium enema	Entire colon	1. Loop ileostomy 2. Total colectomy; ileoproctostomy 7 months later	Alive
Zuelzer	2	M	Scout film showed small bowel loops distended	Entire colon and terminal ileum	Exploratory laparotomy	Died
		F	Not reported	Entire colon	Exploratory laparotomy	Died
Riker	4	—	Not reported	Entire colon	Colostomy	Died
		—	Not reported	Entire colon	Cecostomy	Died
		—	Not reported	Entire colon	Not reported	Died
		—	Not reported	Entire colon and terminal ileum	Not reported	Died
Potts	1	—	Not reported	Entire colon	Transverse colostomy	Died
Hiatt	1	—	Not reported	Entire colon	Ileoproctostomy with total colectomy	Alive
Dorman	4	F	Barium enema normal; scout film showed small bowel distention	Entire colon and terminal ileum	1. Transverse colostomy 2. Terminal ileostomy 3. Ileoproctostomy	Alive
		M	Small bowel obstruction on scout film	Entire colon and terminal ileum	Ileostomy	Alive
		F	Barium enema showed microcolon	Entire colon and terminal ileum	Ileostomy and colectomy	Alive
		F	Barium enema showed microcolon	Entire colon and terminal ileum	Ileostomy and colectomy	Died
Sandegard	1	M	Normal barium enema with high cecum; distended loops of small bowel	Entire colon and terminal ileum	1. Ileostomy at 2½ months 2. Ileoproctostomy and total colectomy at 14 months	Alive
Lee	1	—	Not reported	Entire colon	None	Died

TABLE I.—CONT'D

AUTHOR	NUMBER OF CASES	SEX	ROENTGENOGRAMS	INVOLVEMENT	OPERATION	RESULT
Ehrenpreis	1	F	Barium enema showed microcolon and gaseous distention of small bowel	Entire colon and terminal ileum	1. Exploratory laparotomy, enterostomy with removal of meconium 2. Ileostomy 1 week later	Died
Bill	1	—	Microcolon on barium enema	Entire colon	Not reported	No report
Bodian	1	—	Not reported	Entire colon and terminal ileum	None	Died
Howard	1	F	Narrowed rectosigmoid and proximal dilatation of colon	Entire colon	1. Transverse colostomy 2. Right colectomy with ileotransverse colostomy	Died
Bowden	4	F	Normal barium enema	Entire colon and terminal ileum	Exploratory laparotomy	Died
		F	Microcolon on barium enema	Entire colon and terminal ileum	Exploratory laparotomy at 3 days of age	Died
		M	Distended loops of small bowel on scout film	Entire colon and terminal ileum	Ileocolic anastomosis with resection of lower ileum and cecum	Died
		F	Microcolon on barium enema	Entire colon and terminal ileum	Exploratory laparotomy	Died
Sieber	2	F	Not diagnostic	Entire colon and terminal ileum	1. Exploratory laparotomy 2. Ileostomy and ascending colostomy 10 days later	Died
		F	Not diagnostic	Entire colon and terminal ileum	1. Ileostomy at age 1 month 2. Ileoproctostomy at age 1½ months	Died, age 11 months

the entire colon and the terminal portion of the ileum. A few authors have reported on a substantial number of cases of Hirschsprung's disease.

In 1955 Swenson and Fisher[25] reported on their experience with 150 patients and discussed 2 patients who had the entire colon involved, an incidence of 1.3 per cent. In 1957, Sieber and Girdany[21] reported on 30 cases of symptomatic aganglionic megacolon and noted 2 female infants in whom ganglion cells were absent from the entire colon and terminal ileum, an incidence of 6.7 per cent. In addition, they noted 6 infants in whom the aganglionic segment extended to the transverse colon. Riker,[18] in 1957, reported on 59 cases, in which there had been adequate pathologic examination in 51. He noted aganglionic

involvement of the entire colon in 3 cases, of the entire colon and terminal ileum in 1 case, and involvement up to the duodenum in 2 cases; an incidence of 11.8 per cent. In addition, Riker described 6 cases of aganglionosis up to the splenic flexure and 10 cases of involvement up to the transverse colon. Thus, in 51 cases, only 29 (57 per cent, involved just the rectum or rectosigmoid as in classical Hirschsprung's disease. This is in contrast to the report of Bodian[3] who estimated that the aganglionic involvement is confined to the rectum and/or rectosigmoid in 90 per cent of cases of Hirschsprung's disease, while the remaining 10 per cent are the long segment type. There have also been rare reports of cases of alternating aganglionic segments and normal segments of colon described.[6, 12, 28]

Of the 26 cases of universal aganglionosis which we have collected, the sex of the child was reported in 17 cases. Eleven patients, or 64.7 per cent, were females. This is in marked contrast to the reports in the literature indicating a high incidence of Hirschsprung's disease in the male; for example, Sieber and Girdany[21] reported 83 per cent of cases as being male.

Only 7 of the 26 cases of universal aganglionosis had a successful outcome. Nineteen (73 per cent) died. In a series with the usual involvement of the rectum and/or rectosigmoid plus an occasional long segment type, Dorman[7] collected 156 cases reported in infants under 6 months of age since 1947. The mortality rate in this series was 48.7 per cent. Klein and Scarborough,[13] in a review of 50 cases, reported a 70 per cent mortality rate.

Classical Hirschsprung's Disease.—The clinical findings in an infant generally include a period of abdominal distention, obstipation, and vomiting. Passage of meconium is often absent or scanty. Rectal examination will often be quickly followed by the appearance of meconium. An obstructive series and barium enema in these cases are frequently diagnostic. The positive roentgen findings include dilated loops of small intestine with fluid levels, visualization of the segment of achalasia with proximal dilatation, or considerable retention of the barium on follow-up films taken 24 to 48 hours after the barium enema. The rectal biopsy will confirm the clinical diagnosis by demonstrating the absence of ganglion cells.[27] The biopsy must contain both the outer longitudinal and the inner circular coats of muscle as the normal gangion cells lie between these two layers.

The treatment of these infants by parasympathomimetic drugs, enemas, laxatives, or wetting agents will be effective only in occasional mild cases.[4, 7, 8, 15] The treatment of choice today is to perform a colostomy proximal to the level of aganglionosis as soon as the diagnosis is established. Biopsy is performed at the site of the colostomy to make sure that it is in an area of normal bowel.

Swenson[23] reported a mortality rate of 40 per cent when the establishment of a colostomy was delayed until the patient's bowel became obstructed. After establishment of the colostomy, one should wait until the child reaches 12 to 18 months of age and weighs 20 to 30 pounds.[23] At that time the definitive abdominoperineal pull-through procedure is performed to establish continuity of

the bowel. A mortality rate of 3 per cent was reported by Swenson[22] in a review of his first 200 patients treated by the pull-through procedure. Seven of his patients in a 1- to 5-year follow-up study had died suddenly following illnesses of less than 24 hours' duration. In all but 1, a postmortem examination was made, and infection with severe dehydration proved to be the cause of death. He postulated that there is a defect in the normal mechanisms to combat infection and, in addition, there may be abnormalities in the autonomic control of fluid and electrolyte balance.

Universal Colonic Aganglionosis.—The clinical findings parallel those of patients with classical Hirschsprung's disease, but are more severe and are often bizarre.[25] The defect involves the entire colon and these infants often present with a clinical picture which is similar to that found in small bowel obstruction, meconium ileus, atresia of the small intestine, mid-gut volvulus, among others. Failure to pass meconium is very common.[29] Whereas rectal examinations are often followed by the passage of meconium in classical Hirschsprung's disease, such examinations in infants with universal aganglionosis are very frequently nonproductive in this respect.

Obstructive series commonly demonstrate dilatation of the small bowel with fluid levels, often interpreted as compatible with small bowel obstruction. Barium enemas most often will reveal microcolon or will be interpreted as normal colon.[2, 4, 7, 8, 19, 21] Evacuation of the barium is commonly delayed and barium is present days afterward. Rectal biopsy on these infants, as on patients with classical Hirschsprung's disease, is diagnostic.

At laparotomy, abdominal examination will reveal the presence of normal-sized colon or microcolon, with distended and fluid-filled loops of small bowel. Biopsies of the musculature of the bowel wall should then be performed to determine the presence of ganglion cells. The surgeon should proceed proximally if the biopsy reveals absence of these cells. In universal colonic aganglionosis, an ileostomy proximal to the level of aganglionosis is required. Either a loop or an end-type ileostomy can be performed. A definitive resection with a pull-through ileoproctostomy is indicated when the child reaches 20 to 30 pounds in weight.[23]

Postoperatively, the care of these patients is complicated by frequent liquid bowel movements, often 10 to 15 per day. This diarrhea will respond to dietary management, constipating agents, and local treatment of any perianal excoriations.

The cause of chronic recurrent diarrhea may be related to the fact that these patients still have a defect of ganglion cells which involves the remaining small cuff of rectum. In the follow-up care of these children who have had the pull-through procedure, those patients who have had difficulty in bowel function and who fail to respond to medical therapy are now being treated by a posterior anal sphincterotomy in an attempt to overcome the tightness of the anal sphincters which these patients exhibit.

SUMMARY

1. A case of Hirschsprung's disease is reported in which the entire colon was involved, and in which, when the patient was 20 months of age, total colectomy was completed and an ileoproctostomy performed by the Swenson procedure. The child survived for 2½ years in a good state of health and died in the course of an acute illness manifested by vomiting, diarrhea, abdominal distention, and ulceration of the ileum.

2. Twenty-six cases have been reported in the literature in which the aganglionic involvement had affected either the entire colon or the entire colon and the terminal ileum. The mortality rate in this series was 73 per cent.

3. Of 17 cases in which the sex of the child was recorded, the incidence of females was 11 (64.7 per cent). Our patient was a female baby. This is contrary to the incidence noted in the literature of Hirschsprung's disease in general, in which male preponderance is in the range of 80 per cent.

4. Clinical findings of universal aganglionosis of the colon parallel those with classical Hirschsprung's disease. The onset of clinical symptoms is earlier and often much more bizarre as it often simulates small bowel obstruction. The roentgen findings most often associated with universal colonic aganglionosis are microcolon on barium enema and small bowel dilatation on plain film of the abdomen.

5. Early operation in the management of these cases is imperative. The clinical picture should alert the physician to the diagnosis of Hirschsprung's disease. Roentgen examination, including a barium enema, is often diagnostic. However, a rectal biopsy should be performed to confirm the clinical diagnosis. At operation, biopsies should be taken from the proposed site of decompression. It is important that the decompression be performed proximal to the area of aganglionic involvement. Continuity of the bowel is later established by the Swenson pull-through operation.

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PULMONIC STENOSIS IN THE FIRST YEAR OF LIFE

Results of Surgery

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THE PAST 15 years have witnessed a revolution in the treatment of cardiovascular disease. As diagnostic methods, surgical technique, and anesthesia improved, the frontiers quickly receded. With the advent of hypothermia and extracorporeal circulation, the direct vision repair of complex intracardiac defects and otherwise inoperable lesions became possible. Despite this rapid progress, one of the major problems still confronting the cardiologist and the cardiac surgeon is the management of congenital heart disease in the first year of life.

It has been well established that mortality from congenital heart disease is highest in infancy, and that many of these deaths occur from defects which are amenable to surgical correction or palliation. It has been variously estimated that from 32 to 60 per cent of infants born alive with congenital heart disease are dead within 12 months of birth.[17, 19, 24]

Pulmonic stenosis with normal aortic root was, as recently as 1947, thought to be a rare lesion[30] but more recent information indicates that it may account for as much as 10 per cent of all congenital heart disease.[17] The average age at death is stated to be 21 years,[1] and more than 50 per cent of all the deaths in childhood from this cause occur in the first year of life.

Between 1952 and February, 1959, 13 infants with congenital pulmonic stenosis were operated upon at the Hospital for Sick Children. There were 10 females and 3 males; their ages at the time of operation ranged from 5 days to 10 months, and their weights varied from 3.1 to 10.2 kilograms. The transventricular operation of Sellors and Brock[4, 27] was used on three occasions and the transarterial operation originally devised by Swan[29] was employed in the remaining 10 cases. Regardless of the age of the patient, direct vision transarterial pulmonary valvulotomy under hypothermia with inflow occlusion has been exclusively employed at this institution since August, 1956. The technique and results in our older patients have been reported in a prior communication.[25]

In addition to the cases just mentioned, there were a number of infants operated upon in whom the pulmonic stenosis was but a part of a more complicated defect; these are not included in the present report. However, presumably all of our group had a patent foramen ovale in addition to pulmonary stenosis.

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RESULTS

The patients have been seen for follow-up at periods ranging from 2 weeks to 6 years postoperatively.

Cyanosis.—All of these infants except 1 (12 of 13) exhibited cyanosis ranging in severity from mild cyanosis to marked cyanosis at rest, and 5 of these developed it within the first 24 hours of life. Of the 11 cyanotic infants who survived operation, 9 have had either complete disappearance of cyanosis or a significant reduction in its intensity. One child has slight residual cyanosis at rest which becomes quite marked on crying, and another had early improvement which gradually deteriorated and required reoperation 6 years later.

Murmur.—Preoperatively all of the patients had murmurs which were mostly of moderate intensity and systolic in time. A continuous murmur was rare. The site of maximum intensity was in the pulmonic area in roughly one half of the patients and lower along the left sternal border in the remainder, and the murmur may have had a tricuspid regurgitant rather than a pulmonary stenotic origin. The character and location of the murmur seemed to have little relation to age except that a continuous murmur was heard for 48 hours in the youngest patient in the series, a 5-day-old female infant.

Postoperatively, the changes in the murmurs were not dramatic, by and large. The intensity remained the same or was slightly decreased in most cases; in one child it disappeared altogether. In only one instance did a significantly louder murmur develop after valvulotomy; this was in a child whose clinical result was only fair and whose right ventricular pressure is still elevated. In all cases the location of the murmur was essentially the same.

Electrocardiography.—The youngest patients, both neonates, had electrocardiographic patterns of pure left ventricular hypertrophy. One showed right atrial hypertrophy also. The QRS axes were plus 30 degress and plus 60 degrees.

In the older infants, aged 5 weeks to 10 months, right ventricular hypertrophy was invariable. The height of R in V_1 exceeded 20 mm. in 70 per cent and only 1 infant failed to show a qR pattern in V_1 or V_{3R}. Additional evidence of right atrial hypertrophy was provided in these cases by peaked P waves whose amplitude exceeded 2.5 mm. in all but 3 instances. The axis of QRS lay between plus 90 degrees and plus 170 degrees. Evidence to suggest associated left ventricular hypertrophy (q in V_6 of 2 mm. or more) existed in 2 patients.

Immediate changes in the electrocardiogram were uncommon after surgical therapy. The newborn infants continued to show left ventricular hypertrophy, 1 for longer than 6 months, despite very adequate right ventricular pressure reduction. Although a few became normal within 6 months, most showed reduction in voltage in RV or other signs of lessening of right ventricular hypertrophy for a minimum of 6 months. Abnormal tracings were longer where the surgical result was unsatisfactory.

Physiologic Data.—Eight patients had preoperative heart catheterizations (Fig. 1). The systolic right ventricular pressure varied from 125 to 165 mm. Hg (average 140). The right atrial oxygen saturation ranged from 10 to 55

per cent (average 26 per cent). All of these patients survived, 7 of them were recatheterized postoperatively, and 2 more had postoperative catheterization only. These studies were performed at intervals of 2 weeks to 5 years postoperatively, and none of the figures shown in Fig. 1 represent values obtained at the time of surgery or with the patient under general anesthesia. The postoperative right ventricular pressures varied from 27 to 80 mm. Hg (average 51), and the mean reduction in right ventricular pressure was 95 mm. Hg. The Pulmonary artery was entered on only 5 occasions during the follow-up studies, and the mean residual systolic gradient across the valve was 24 mm. Hg (range 17 to 30).

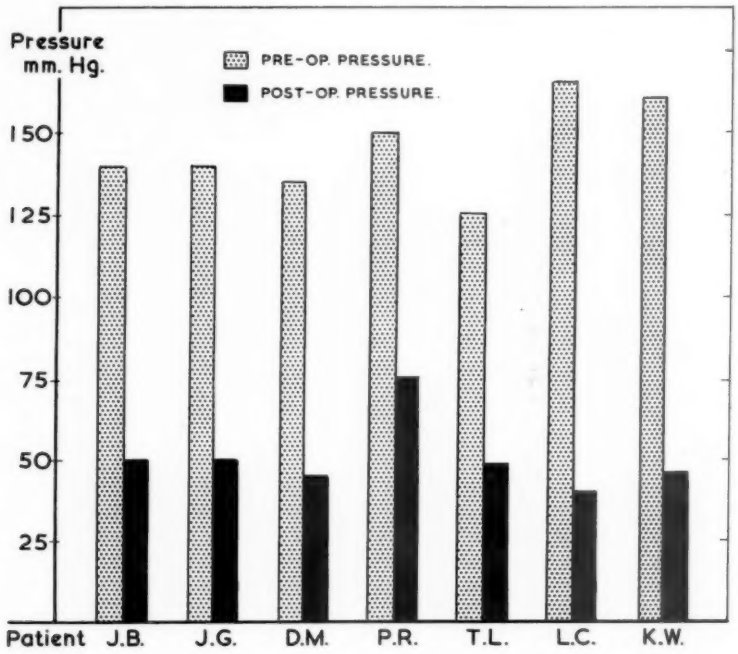

Fig. 1.—Seven documented cases of right ventricular pressures (catheterization not done at time of operation).

Mortality.—There were 2 deaths; 1 of these was in a female infant, weighing 5.1 kilograms, who was operated upon at the age of 9 months because of cyanosis since birth. She died at operation shortly after the completion of a transventricular valvulotomy. An autopsy showed a valvular and high infundibular stenosis to be present, and, in addition, it was also noted that the knife that had been used to cut the valve prior to dilation had missed the valve completely and had cut into the mediastinum instead! The other fatality was a male, weighing 5.5 kilograms, who had suddenly developed cyanosis at the age of 3 months and had undergone transventricular valvulotomy shortly thereafter. A preoperative right ventricular pressure was 150/10 mm. Hg. A transventricular valvulotomy was done with moderate clinical improvement, but the right ventricular pressure 3 years later was 75/10 mm. Hg. Because of severe, progressive neurologic disease, unrelated to his cardiac lesion, further surgery was not performed. He has since succumbed to this latter condition, and an autopsy performed elsewhere showed a 3 mm. pulmonary valve orifice.

Over-all Results.—It seemed worth while to try to arrive at some evaluation of the over-all success of these operations, and a variety of factors were taken into consideration, some of which have just been discussed. The criteria which we applied were (a) unequivocal improvement in cyanosis or its complete disappearance, (b) reduction of the postoperative right ventricular pressure to 50 mm. Hg or less, and (c) obvious improvement in the infant's general condition and well-being. Although this last criterion is subjective, attention should be drawn to the fact that, in contradistinction to older children and adults in whom pulmonic stenosis is minimally symptomatic and operation elective, many of these infants were seriously ill and probably doomed to death without operation, which was performed in some cases on an emergency basis. The results of this synthesis of our data are categorized into "satisfactory, partially satisfactory, and death." The data indicated that a totally unsatisfactory result, due to the severity of the lesion encountered, was tantamount to a fatality, hence the above classification. Nine patients were considered to have had a satisfactory result, 2 patients to have had only a partially satisfactory result, and 2 died.

It should be noted that all results classified as satisfactory followed transarterial valvulotomy under hypothermia with inflow occlusion, regardless of the age or size of the patient. Although our series is small, it nevertheless may be quite significant that in our hands no satisfactory result followed transventricular valvulotomy.

COMMENT

Congenital pulmonic stenosis is now frequently recognized and is one of the most rewarding lesions with which the surgeon must deal. Numerous reports of successful operaton on this defect are now available in the literature,[2, 3, 5-15, 18, 20-23, 26, 28] but the majority of patients hitherto reported were older children and adults, and it would appear that experience in the management of pulmonic stenosis in infancy is still limited. There has been little emphasis in the literature on the special problems of recognition and treatment of this condition in infancy, although Johnson and Johnson[16] in reporting 5 postmortem cases of pulmonic stenosis with patent foramen ovale believe that a timely valvulotomy might prove lifesaving to such babies. This point of view has since been re-asserted by Gibson,[11] Moss,[21] and Collins[6] and their colleagues, and is one of our major reasons in reporting the present series.

We have been able to cull a total of 19 cases from the literature (Table I) but, in view, of the frequency with which pulmonic valvulotomy is now being performed, there must be numerous other unreported cases.

Physical findings encountered in our older infants exhibit no major differences from those found in older children and adults with the disorder. The main danger in the severe cases in infants, as suggested by Johnson and Johnson,[16] is a failure to instigate operative assistance as an emergency measure in a baby who may not look seriously ill.

The newborn infant with severe pulmonic stenosis and normal aortic root poses a more difficult diagnostic problem. Cyanosis, giant "a" waves in the jugular venous pulse, and reduced lung vascularity at fluoroscopy may be the

TABLE I

	CASES	DEATHS	OPERATION
Gross (1956)	1	1	Transventricular
Hosier (1956)	2	?	Transventricular
Swan (1957)	1	1	Transarterial
Hanson (1958)	1	0	Transventricular
Moss (1958)	1	0	Transventricular
Humphreys (1954)	1	0	Transventricular
Gibson (1954)	8	1	Transventricular
Collins (1959)	4	0	Transventricular
The Hospital for Sick Children (1959)	14	2	
Totals	33	5 (16%)	

only signs common to these and older age groups. In the newborn there is frequently a harsh, early systolic murmur, but it is not always localized to the second left intercostal space and may be of very short duration, ending well before an accentuated second sound (aortic). In a few cases there may be no murmur, or a continuous murmur may mark an underlying ejection systolic murmur. The electrocardiogram will show either right ventricular hypertrophy or left ventricular hypertrophy with right atrial hypertrophy. In the presence of these signs, the differential diagnosis rests clinically between tricuspid atresia, pulmonary atresia with normal aortic root, pulmonary stenosis with normal aortic root, and tetralogy of Fallot with rudimentary right ventricle. Angiocardiography, particularly selective injection of contrast medium into each ventricle utilizing cinematic techniques, offers the best chance of differentiating pulmonic atresia or pulmonic stenosis with normal aortic root; but, more important, it allows determination of right ventricular chamber size, the anatomic feature governing the success or failure of the treated cases. Because of the less clear-cut clinical picture and the greater range of diagnostic possibilities in the newborn, prompt elucidation of the malformation by available techniques and surgical treatment of suitable patients should be an urgent matter.

SUMMARY

1. Congenital heart disease is still a leading cause of death in infants and children, and the mortality is highest in the first year of life.

2. Thirteen pulmonic valvulotomies have been performed at the Hospital for Sick Children for infants of less than one year of age for pulmonic stenosis with normal aortic roots, with only two fatal outcomes.

3. All of these patients except one exhibited some degree of cyanosis and all had a murmur. There was electrocardiographic evidence of right ventricular hypertrophy in all but the 2 youngest babies in the group, both neonates who showed a pattern of left ventricular hypertrophy. Right atrial hypertrophy was a frequent additional finding. Eight had preoperative right heart catheterizations and the right ventricular pressures ranged between 125 to 165 mm. Hg.

4. Nine of the surviving patients have had a satisfactory result and 2 a partially satisfactory result. Clinical and physiologic data to support this contention have been presented.

5. Transarterial valvulotomy under direct vision with inflow occlusion and hypothermia has been more uniformly successful in our hands than a blind transventricular approach, regardless of the age, size, or preoperative condition of the patient.

6. Pulmonic stenosis with normal aortic root can be a lethal lesion in infancy, and its investigation and treatment should be urgent matters. Selective angiocardiography utilizing cinematic techniques offers the best chance of elucidation of the character of the defect.

7. There has been relatively little emphasis in the literature placed on the problems of pulmonic stenosis in the first year of life. Nineteen cases with 3 deaths have been collected from a number of reports dealing with results of surgery for this lesion, but in view of the frequency with which such operations are now being performed it would seem that there must be many other unreported cases.

ADDENDUM

One additional patient, age 2 months, has undergone transarterial valvulotomy since this report was prepared and was doing well 2 weeks postoperatively.

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GASTROINTESTINAL BLEEDING AFTER CARDIOVASCULAR OPERATIONS IN CHILDREN

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PEPTIC ULCER is relatively rare in children, but the association of gastroduodenal erosion with severe burns,[8, 14] central nervous system lesions,[6, 9] and adrenocortical or ACTH therapy[3, 16, 25] is well established. The extensive surgical insults, which may now be survived through the use of current supportive adjuncts, occasion renewed interest in the syndrome of stress ulcer. Four patients in the pediatric age group, recently subjected to cardiovascular operations at the National Heart Institute, have exhibited gastrointestinal bleeding ascribed to this lesion. Brief summaries of their courses and considerations of the etiology and management of acute stress ulcer are included in the present report.

CASE REPORTS

CASE 1.—D. D. (Clinical Center No. 01-01-14), a 4-year-old boy, had been known to have a heart murmur since birth. He had experienced frequent respiratory infections and his growth and development were poor. The clinical findings were those of ventricular septal defect and this diagnosis was confirmed by right heart catheterization. Through a median sternotomy, the defect was closed by direct suture during complete cardiopulmonary bypass (20 minutes) and a period of elective cardiac arrest induced with potassium citrate (15 minutes). His early postoperative course was characterized by mild hypotension and subsequently by moderate temperature elevation. On the fifth and sixth postoperative days the child passed many tarry stools and the hemoglobin fell from 12.5 to 9.8 Gm. per 100 c.c. Bleeding ceased when a bland diet and antacids were administered.

CASE 2.—P. DeG. (Clinical Center No. 02-16-49), a 6-year-old girl, had been cyanotic since birth, exhibited characteristic clubbing of fingers, squatted frequently, and was subject to frequent convulsive seizures. The clinical findings were consistent with tetralogy of Fallot and this diagnosis was substantiated by right heart catheterization. A selective angiocardiogram disclosed an extremely hypoplastic right ventricular outflow tract and the lesion was not considered amenable to complete correction. A left subclavian pulmonary artery anastomosis was performed through a left posterolateral thoracotomy. On the day following operation, she vomited coffee-ground material and a decrease in hemoglobin from 22.8 Gm. per 100 c.c. to 19.6 Gm. was detected in the ensuing 24 hours. The child complained of cramping epigastric pain and the upper abdomen was tender to palpation. All symptoms subsided when milk, cream, and antacids were administered and there was no evidence of further bleeding.

CASE 3.—E. S. (Clinical Center No. 02-07-18), a 5-year-old boy, had a heart murmur which had been detected soon after birth. He was subject to frequent upper respiratory infections and developed poorly. The clinical findings were characteristic of atrial septal defect, and the diagnosis was confirmed by right heart catheterization. The lesion was repaired by direct suture during cardiopulmonary bypass (25 minutes) and the child's

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immediate postoperative condition was good. Approximately 8 hours later, however, acute complete laryngeal obstruction resulted from mucus. A tracheostomy was immediately carried out, but during the hypoxic episode cardiac arrest occurred. A left thoracotomy was performed and resuscitation was successful. There were no neurologic sequelae. On the fifth postoperative day marked pallor and slight tachycardia were noted, and the child passed the first of several tarry stools. The hematocrit fell from 35 to 20.6 and was corrected by transfusion. Milk, cream, and antacids were administered and bleeding appeared to cease. X-rays of the abdomen showed no abnormalities until the eighth postoperative day when free intraperitoneal air was first noted. However, the abdomen was soft, peristalsis was audible, and the child appeared to be improved. Management by means of nasogastric suction was elected. On the eleventh postoperative day the blood pressure fell precipitously and he again passed several large tarry stools. Blood was replaced and an abdominal exploration was promptly performed. A perforation, sealed by omentum, was found immediately below the pylorus on the anterior surface of the duodenum. The stomach and small intestine were distended with fresh blood which was issuing from the edges of the actively bleeding ulcer. The hemorrhage was controlled by sutures which also closed the perforation transversely. Cardiac arrest occurred during closure of the abdomen and attempts at resuscitation were unavailing.

No additional findings of significance were disclosed by autopsy, except for retarded healing and remarkable lack of reaction about the incisions. Permission for examination of the brain was not granted.

CASE 4.—J. P. (Clinical Center No. 02-20-60), a 17-year-old girl, had been known to have heart disease from the age of 3 months. Growth and development were normal but she complained of increasingly severe dyspnea and fatigability. The clinical findings were those of ventricular septal defect and this was confirmed by right heart catheterization. There was marked pulmonary hypertension but no right-to-left shunt was detected. The ventricular septal defect was closed by direct suture during cardiopulmonary bypass and a period of anoxic cardiac arrest. The duration of arrest was 9 minutes and perfusion was maintained for a total of 48 minutes.

The arterial blood pressure was unstable immediately following operation and Aramine was slowly infused for approximately 12 hours. There was also a moderate febrile reaction. On the third postoperative day the patient passed several tarry stools and the hematocrit was noted to fall from 50 to 38. During the period of active bleeding the total eosinophil count was 300. She was placed on a diet of milk and cream. Antacids were administered and the blood loss was replaced by transfusion. No further bleeding occurred.

DISCUSSION

Cushing[9] called attention to the coincidence of cerebral lesions and erosions of the upper digestive tract, and he attributed the ulcers to vagal stimulation of gastric secretion. Although the occurrence of peptic ulcer with the shock or exhaustion phases of the alarm reaction[24] is generally appreciated, the precise mechanism of gastroduodenal ulceration mediated by the hypothalamic-pituitary-adrenocortical axis is controversial. Increased gastric secretion of acid and pepsin has been implicated by some investigators,[26, 30] while others[15, 19] have elicited no stimulation of gastric secretion by ACTH or adrenal steroid administration. Janowitz and his co-workers[17] have demonstrated retarded healing of wounded gastric explants in the dog, and postulate impaired defensive and reparative processes as of prime importance. Brown and his colleagues[4] have reported the association of gastrointestinal bleeding with excessive endogenous or exogenous circulating pressor amines in 2 patients and have demonstrated experimentally the relationship between

norepinephrine administration and necrotizing gastric and mesenteric arteritis. Gastroenterologists[13] make the pratical observations that inadequate oral intake in stressful situations prevents the periodic neutralization of gastric secretions and interdicts normal gastrointestinal physiology.

Interest in stress ulceration has been directed principally to the association of this phenomenon with central nervous system lesions, burns, or ACTH or adrenal steroid administration, although there are scattered references to its occurrence following surgical trauma.[1, 11, 12, 20] Gastroduodenal erosion is a relatively frequent autopsy finding[22, 29] and is usually held to be an agonal event. Harkins' comprehensive review of "Curling's ulcer"[14] supplies several interesting statistics: The average age of 74 patients in which this information was specified was 14.6 years. In 91 patients studied at autopsy the duodenum alone was involved in 71, the stomach in 16, and both in 5. Solitary ulcers occurred in 57 patients, while the ulcers were multiple in 34. Death resulted from hemorrhage twice as frequently as from perforation. According to Weigel and associates,[28] hemorrhage occurs most commonly on the eighth to tenth day following the traumatic experience, although it has been noted as early as 3½ hours afterward or as late as several weeks.[13] The mortality directly attributable to these acute gastrointestinal lesions is difficult to ascertain because of the usual gravity of the primary process.

In the management of stress ulcer the necessity for adherence to a medical regimen of diet and antacids has been reiterated,[3, 5, 13] but no surgical indications peculiar to this lesion have been described. Similarly, the literature does not distinguish the surgical implications of hemorrhage in stress ulcer from that occurring with chronic peptic ulcer. There is no report of a single sizeable experience with operative intervention for acute gastroduodenal ulceration in children, although Bird and his colleagues[2] studied 119 surgical patients described in the literature and McAleese and Sieber,[21] 24. Twelve in the former review and 7 in the latter were explored because of hemorrhage; there was no elaboration of the indications for operation.

At the National Heart Institute, gastrointestinal hemorrhage after cardiovascular surgery has been observed only in children. Approximately 250 operations in this age group have been carried out, 100 by open and the remainder by closed techniques. The only factor common to all 4 patients described was the general nature of the surgical trauma. Physiologic arterial and venous pressures, electroencephalographic tracings, and blood oxygen tension and electrolytes were maintained throughout the operations. The perfusion rate (2.2 L. per minute per square meter^2) and arterial oxygen tension (150 mm. Hg) were normal throughout each of the 3 operations carried out with cardiopulmonary bypass. The child in whom the anastomosis was performed experienced no evident period of anoxia. Each patient reacted promptly upon termination of anesthesia, and none demonstrated a neurologic or metabolic defect. Although complete cardiopulmonary bypass and total body perfusion unquestionably inflict a massive insult, the homeostatic responses evoked by the procedure have not been comprehensively assessed.

All of the children were unusually apprehensive before hemorrhage was evident, but there were no specific premonitory symptoms or signs. The episodes of bleeding occurred between the first and fifth postoperative days and were first indicated by hematemesis in 1 patient and melena in 3. An ulcer regimen, consisting of milk and cream feedings, antacids, careful sedation, and supportive blood transfusions was instituted immediately after bleeding was detected in each patient. This form of management proved effective in three instances but afforded only temporary improvement in the fourth patient who died following perforation and a second exsanguinating hemorrhage. Peptic erosion of the upper digestive tract was the presumed site of bleeding in all and this site was proved at autopsy in 1. Of particular interest was the gross impairment in wound healing evident in the latter instance. The lack of reaction about sutures and the edges of incisions and the terminal dehiscence of the thoracotomy were consistent with the retarded reparatory processes occasionally associated with massive adrenal steroid therapy. It is noteworthy that but 1 of the 4 patients received vasopressors.

The obscure mechanism and occult nature of stress ulcer frustrate attempts at prophylaxis. An awareness of the entity, careful observation of postoperative patients for melena or fall in hematocrit, and prompt treatment afford the only means of protection. The postoperative alimentary routine at the National Heart Institute has been consistent and on the whole satisfactory. Graduated oral intake is begun when the patient desires it and has normal peristalsis, usually by the second postoperative day.

The tabulation of indications for operation in bleeding stress ulcer, similar to those advanced relative to peptic ulcer[10, 18] is hindered by several considerations: the cumulative reported experience is as yet inadequate, the basic mechanism of stress ulcer is not completely understood and may differ materially from that of "spontaneous" peptic ulceration, and its occurrence in children also involves distinct problems. Unequivocal indications for abdominal exploration suggest themselves: hemorrhage of sufficient magnitude to produce systemic hypotension, continuing significant blood loss over an 8- to 12-hour period, recurrence of bleeding after cessation, and the coincidence of hemorrhage and perforation.

The technical repertory applicable in the operative management of postoperative gastroduodenal hemorrhage in children is limited. The nutritional sequelae incident to gastric resection or vagotomy and the acute transient nature of the stimulus to ulcer formation would seem to militate against the performance of these procedures. On the other hand, the precarious condition of the patient demands that hemostasis be prompt and secure. It would seem that if abdominal operation is undertaken, the definitive procedure must be elected at the time, the above considerations and the state of the individual patient being the principal determining factors. If positive control of bleeding can be accomplished by simple excision and closure of a discrete ulcer, this operation is probably the method of choice. Direct suture was employed in the 1 patient in whom laparotomy was necessary. The favorable outcome of nonoperative

management in the 3 patients described indicates that this form of treatment should be instituted as a primary measure in every child and will result in cessation of bleeding in many instances. The possible roles of adrenal suppression[7, 23] or local gastric cooling[27] must remain speculative.

Massive surgical undertakings such as cardiopulmonary bypass in the treatment of heart disease, extensive ablation of malignancy, and contemplated transplantation techniques emphasize the importance of the endocrinology of trauma. Whatever may be the ultimate homeostatic and reparative functions mediated by the hypothalamic-pituitary-adrenocortical apparatus, it is manifest that their unbounded participation in stress may constitute a hazard to recovery.

SUMMARY

Four patients who exhibited gastrointestinal bleeding after cardiovascular operations are described. The mechanism of gastroduodenal ulceration following trauma and the surgical implications of hemorrhage from stress ulceration are discussed. Special limitations encountered in operating upon children with bleeding stress ulcer are defined and the need for expedient conservative operation is emphasized.

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Editorials

CONDUCTED BY I. S. RAVDIN, M.D., AND J. GARROTT ALLEN, M.D.

Re-evaluation of the Activities of SURGERY

In order to serve the readers better, the Editorial Board of SURGERY undertook to determine what changes in editorial policy, if any, were desired by its subscribers. To accomplish this, an elaborate questionnaire was prepared and sent to all subscribers. In this way an attempt was made to determine what kind of material readers desired in regard to the area involved, such as gastrointestinal and cardiovascular, and also in regard to the subjects, such as cancer, preoperative and postoperative care, physiology, research, and so on. The replies were classified according to individual and institutional subscribers, both domestic and foreign.

An over-all response of 70 per cent was obtained, which astonished and greatly pleased the Editorial Board and Editors. The questionnaires were apparently considered very carefully, as evidenced by the fact that not a single respondent requested "greater coverage" in every subject. Of those replying, 87 per cent were general surgeons and 16 per cent were specialists of those living in foreign countries, these respective percentages were 68 and 32. Of those practicing in the United States, 48 per cent were in private practice only, 36 per cent were in part-time teaching, 10 per cent in full-time teaching, and 9 per cent were residents. Of the foreign subscribers, 31 per cent were in private practice only, 59 per cent were in part-time teaching, and 10 per cent in full-time teaching. Among the domestic subscribers, the majority desired full or some coverage of the following subjects: cancer, 86 per cent; physiology, 81 per cent; preoperative and postoperative care and traumatic surgery, each 78 per cent; shock, 71 per cent; infections in surgery, 71 per cent; burns, 68 per cent; office surgery, 59 per cent, and research, 51 per cent. Interestingly enough, the order of preference of professors of surgery was very little different, that is, cancer, 86 per cent; physiology, 84 per cent; preoperative and postoperative care, 80 per cent; infections in surgery, 72 per cent; shock, 71 per cent; traumatic surgery and research, each 71 per cent, and burns, 61 per cent. The replies to the question concerning the specialty and operating area showed the following: gastrointestinal, 93 per cent; peripheral vascular disease, 91 per cent; proctologic surgery, 86 per cent; varicose veins, 85 per cent; hand surgery, 84 per cent; thoracic surgery, 83 per cent, and cardiovascular surgery, 82 per cent. The preferences of the professors of surgery were: gastrointestinal,

88 per cent; thoracic surgery and cardiovascular surgery, each 85 per cent; peripheral vascular diseases, varicose veins, and hand surgery, each 73 per cent. Obviously, many requested more coverage on several subjects.

Concerning the editorial policy, 28 per cent requested publication of more clinical papers, 12 per cent desired more papers on new techniques, and 4 per cent suggested that the JOURNAL be limited to general surgery coverage. Thirty-two per cent requested continuation of the Reappraisal Section and 3 per cent thought too much space was devoted to cardiovascular surgery.

The survey represents a great deal of work on the part of the publishers, the Editorial Board, and the readers who so thoroughly answered the questions. It is only through constructive criticisms and suggestions that SURGERY can be improved, and we are greatly pleased with the tremendous response, which demonstrates the genuine interest of our readers. Thank you for your cooperation.

Alton Ochsner

Russian Gall Bladder Surgery According to Ossipov

The issue of SURGERY for September, 1959, contains an article by Dr. B. K. Ossipov[2] of Moscow, describing methods and results of treatment of acute cholecystitis in Russia. Many features of this report should be of interest to American readers. Notable among these is the fact that the author, in comparing results of treatment of acute cholecystitis in Russia with those in America, has apparently misunderstood and misquoted two American publications to which he refers. These errors, which should be rectified, reflect the difficulties in communication of ideas occasioned by the great differences in the languages of our respective countries.

The author introduces his subject by calling attention to the lack of a uniform opinion in Russia concerning the indications for surgical treatment of acute cholecystitis. Between the years 1951 and 1954, when early surgical treatment was uncommon, the over-all operative mortality rate in 25 Moscow hospitals was 11 per cent, varying from 7.75 to 19.5 per cent in individual hospitals.

In an effort to improve these results and to establish a more effective plan of treatment, the Sixth Plenary Session of the Board of the All-Union Surgical Society devoted much of its meeting in November, 1956, to the problem of acute cholecystitis. Since that time the author has employed a policy of earlier operation, with improvement in his results. As in the past, he has continued to employ local infiltration, paranephric, and splanchnic block anesthesia in most cases. This technique, which is described in detail, was utilized in 274 of 285 operations for acute cholecystitis. Cholecystectomy was accomplished on all patients in this series, with a mortality rate of 3.15 per cent. This compares favorably with results achieved in the United States.

With regard to the results of treatment of acute cholecystitis in other countries, Dr. Ossipov cites only one American reference, as follows: "Analyzing their material relating to the surgical treatment of acute cholecystitis, Pines and Rabinovitch[3] point out that the prognosis is better when the interval between

the attack of the disease and the operation is shorter. Thirty of their patients were hospitalized shortly after an attack of the disease but were operated upon within a period of 3 to 27 days after admission. The mortality rate was 20 per cent." This is quoted out of context by Dr. Ossipov. While Pines and Rabinovitch did make such a statement, their study dealt specifically with perforation of the gall bladder, and the 30 patients to whom they referred had all suffered this complication.

The author expresses enthusiasm for operative cholangiography, stating that "as a rule during the operation we employ cholangiography which was elaborated in our clinic by Dr. E. M. Perkin." After some additional comments on cholangiography and manometry, a second reference to the American literature is presented as follows: "Claude E. Welch, who thoroughly studied the literature pertaining to this problem, refers to the results of cholangiography performed in 110 patients 10 days after the operation. The cholangiograms showed that, in 20 per cent of all cases, the common bile duct contained stones which had been overlooked during the operation. The author has also observed 100 cases operated upon by him personally. In all these cases no cholangiography was performed during the operation, but postoperative cholangiography performed 7 to 10 days after operation revealed in 53 cases the presence of stones in the common bile duct." The first portion of this quotation, relative to 20 per cent residual stones in 110 patients, is correct, and was derived by Welch from a report published by Hicken, McAllister, and Call.[1] The second portion, however, dealing with Welch's own series of 100 cases, is incorrect, both with regard to figures and to Welch's interpretation and conclusions. The purpose of this study by Welch was to emphasize the technical steps whereby the surgeon, unaided by the radiologist, could reduce to a minimum the number of stones left in the common duct at operation. His own results are reported as follows: "The author accordingly has reviewed 100 personal consecutive cases in which the described technique was followed, operative cholangiography was not used, and postoperative cholangiograms were done in all cases 7 to 10 days later. Stones had been found in some portion of the biliary system in all; in 53 cases they were present in the common duct. In only one instance—and here the operation was discontinued after an arduous transduodenal exploration with the full recognition of the fact that there was still a stone imbedded in the head of the pancreas—was there evidence of a retained stone." Thus, the correct figure for retained stones in Welch's series is 1 per cent, rather than 53 per cent as stated by Dr. Ossipov. In his conclusion, Welch states that "it seems reasonable to conclude that the surgeon who wishes to reduce the number of retained stones can accomplish this purpose more effectively by first perfecting a sound surgical technique rather than by compromising with radiologic substitutes." This differs significantly from the conclusion attributed by Ossipov to Welch, which is as follows: "the author concluded that the expediency of applying cholangiography during the operation can in no way be denied; at the same time, however, he rightfully emphasizes that the operating surgeon must constantly perfect his technical skill."

Reports of Russian authors such as that of Dr. Ossipov are of great interest, and their publication in this country should be encouraged. In medicine, as in other fields of science, government, and human affairs, it is desirable that we and the Russians seek to understand one another more clearly. These corrections are submitted in the interest of accuracy and mutual understanding.

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Surgical History

CONDUCTED BY JOHN R. PAINE, M.D.

THE HISTORICAL DEVELOPMENT OF MEDICAL EDUCATION IN THE UNITED STATES

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THE COLONIAL ERA

PRIOR to 1765 there were no schools of medicine in the Colonies and the vast majority of physicians practicing medicine had become qualified by serving a 2- or 3-year preceptorship under a practicing physician. An occasional wealthy student was able to travel to the British Isles or the Continent to receive conventional medical training at a university. During this era there was very little legislation to control the practice of medicine; the earliest known legislative act was passed in Virginia in 1639. This was designed to prevent the charging of excessive fees. Shortly before the Revolution, according to Smith,[11] conditions were so bad that he quotes: "Few physicians among us are eminent for their skill. Quacks abound like locusts in Egypt and too many have recommended themselves to a full and profitable practice and subsistence. This is the less to be wondered at, as the profession is under no kind of regulation. Loud as the call is, to our shame be it remembered that we have no law to protect the lives of the King's subjects from the malpractice of pretenders. Any man at his pleasure sets up for a physician, apothecary, and surgeon; no candidates are either examined or licensed, or even sworn to fair practice."

An exception was the colony of New York, where in 1760 the practice of medicine was controlled by an examination in physic and surgery, as seen by the following quotation from Flaherty[3]: "No person whatsoever shall practice as a physician or surgeon in the said City of New York before he shall first have been examined in Physic and Surgery and approved of, and admitted by one of his Majesty's Council, the Judges of the Supreme Court, the King's Attorney-General and the Mayor of the City of New York for the time being, or by any three or more of them, taking to them assistance for such examination as they in their discretion shall think fit." A similar law was passed in New Jersey in 1772.

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The beginning of formal medical education in the Colonies was the establishment of the College of Philadelphia by John Morgan and William Shippen in 1765. In 1768 they conferred the first degree of Bachelor of Medicine on one of their graduates. The medical school of King's College in New York was founded in 1768 and here the first Doctor of Medicine degree was awarded in 1770.

At the time of the Revolution there were 3,500 practicing physicians among the 3,000,000 population of the Colonies. Of this number, 400 had M.D. degrees, 51 of them having graduated from an American school. Other schools were founded at Harvard in 1782 and Dartmouth in 1797.

After the Revolution the spirit of liberty and freedom in the Colonies was so intense that efforts to control the practice of medicine were greeted by almost universal opposition. Again in the expanding pioneer society the necessity for having adequate numbers of doctors was so overwhelming that little attention was paid to their medical training.

THE ERA OF PROPRIETARY MEDICAL SCHOOLS

The second phase in the development of medical education came in 1806, when the New York State legislature passed a law incorporating the medical society of the State of New York, which authorized physicians in each county to form local societies which were given the power to grant licenses to practice medicine. The result of this legislation was that the local medical societies not only had the power to grant licenses but also qualified them to establish medical schools apart from the universities. The first of these so-called proprietary medical schools was founded in New York in 1807; it was called the College of Physicians and Surgeons. It was not until 1860 that this eclectic branch became incorporated into Columbia University. The same year a medical school was started in Maryland as the School of Medicine of the University of Maryland, again having no connection with the university.

The appeal of these proprietary schools immediately became apparent, for in contrast with the few struggling medical schools under university supervision, these proprietary schools abandoned the long preliminary education required to enroll in the medical school. They shortened the term of the lectures to 3 to 4 months per year, and they abandoned the concept of awarding two degrees, namely the Bachelor of Medicine and the Doctor of Medicine. Most of the proprietary medical schools required a 2-year preceptorship under the guidance of a practicing physician, together with a lecture course lasting from 12 to 16 weeks.

The popularity of these schools is reflected in the number of medical schools founded at varying periods which endured for an appreciable period of time. There were but four schools of medicine founded between 1765 and 1800. Between 1801 and 1825 the number was increased by twelve. Between 1826 and 1850 nineteen new schools were started, and between 1851 and 1875 twenty-nine new schools made their appearance. Between 1876 and 1900 eighty new schools opened their doors for enrollment. As early as 1826 the medical societies of

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both Vermont and New Hampshire called for cooperative action to rescue the profession from the swarms of physicians being cranked out by "diploma mills."

In 1846 the first efforts were made to establish the American Medical Association, whose object as noted in the declaration of purpose was: "To cultivate and advance medical knowledge; to elevate the standards of medical education; promoting the usefulness, honor, and integrity of the medical profession; enlightening and directing public opinion in regard to the duties and responsibilities and requirements of medical men; for exciting and encouraging emulation and concert of action in the profession and fostering friendly intercourse between those engaged in it."[2]

The first session of the American Medical Association was held in Philadelphia in 1847 and Nathan Smith Davis, who was one of the prime movers for the organization of the society, recommended that the following steps be taken in order to improve medical education: (1) that the course of lectures be prolonged from 4 to 6 months, (2) that there would be sequence and grading in the curriculum, (3) that there would be a separation of the licensing function from the teaching, and (4) that better preliminary education requirements be instituted.

There was great controversy at the time and since the American Medical Association had no legislative powers or control over the functions of the individual states, little was done other than to pass resolutions. In 1858 the Committee on Medical Education recommended that the M.D. degree be offered only after 3 years of study, which would include two sessions of lectures of 6 months each, 3 months of dissection, and one session devoted to hospital attendance during the period of preparation.

Again in most instances the recommendations fell on deaf ears in the individual states. Examples of the widespread lassitude are to be found in legislation in Georgia and South Carolina. In 1826 the State of Georgia created a Board of Examining Physicians and imposed a penalty of $500.00 on any person practicing medicine in Georgia without its license. In 1835 this law was repealed, probably because of the influence of the "botanic" physicians, for in 1839 another act created a Board of Medical Examiners, but with the clause "provided nothing in the said revised act be so construed as to operate against the Thompsonian or botanic practice or any other practitioners of medicine in the State."[3] The legislature of South Carolina passed a law in 1817 creating two Boards of Medical Examiners, one at Charleston and the other at Columbia. All persons practicing medicine in the state were required to receive a license from them except those who possessed a diploma from a medical college. In 1838 the legislature passed another act, abolishing the Boards of Medical Examiners and removed all restrictions on the practice of medicine in South Carolina.

The American Medical Association passed a resolution in 1852 that no medical college could send delegates to the American Medical Association meeting unless it (1) had six members on the faculty, (2) gave one course of instruction annually of not less than 16 weeks in anatomy, materia medica, medicine,

surgery, midwifery, and chemistry, and (3) required that candidates for graduation be 21 years of age, had studied 3 entire years, two of which must have been with some respectable practitioner, having attended two full courses of lectures not in the same year, one of which must have been in the institution granting the diploma, and shown by examination that they were qualified to practice.

Despite all of these high-sounding resolutions, the standards of medical education in this country remained low and the first ray of hope appeared with the founding of The Johns Hopkins Medical School in 1893. Daniel C. Gilman, president of Johns Hopkins University, and John Shaw Billings were responsible for the organization of a great experiment in medical education. They required that applicants to the medical school not only have an undergraduate degree but also that they have special premedical education. They were instrumental in drawing together that fabulous full-time staff—Welch, Osler, Halsted, and Kelly, all of whom are pre-eminent in the history of medical education in the world. The concept of a full-time staff and bedside teaching by the professor was revolutionary in American medical education. To Dr. Halsted goes credit for the first organized residency in general surgery.

Although the American Medical Association had to cast its influence on medical education by suggestion rather than by powers of legislation, it too attempted to improve the situation by the following acts. In 1899 the first survey of the medical schools of the United States was carried out and the first educational number of the *Journal of the American Medical Association* was published in 1901 containing statistics regarding medical education. In 1901 the laws of the various states regulating the practice of medicine were published in a yearly issue. By this time most of the states had established Departments of Health which were authorized to grant a license to practice medicine within the individual states. However, most of these departments were politically controlled and the practice of medicine was still in a very much disorganized state. In 1903 the *Journal of the American Medical Association* tabulated the results of the examinations given by the various state boards and have continued to do so yearly in the State Board Issue. In 1904 the Council on Medical Education and Hospitals was organized and was a forward step in the reformation of the standards of American medical practice. Representatives of the Council of Medical Education and Hospitals conducted surveys of the various medical schools; but because of the great animosity caused in various schools by the preliminary results of these surveys, they were not published until the Carnegie Foundation was approached to act as a disinterested party in conducting a new survey. This was done in 1908 by Abraham Flexner, who represented the Carnegie Foundation, and N. P. Colwell, secretary of the Council of Medical Education and Hospitals. The famous Flexner report[4] appeared in 1910; and although this too had no binding authority to compel the various schools to change their practices, its moral effect was soon forthcoming.

THE MODERN ERA

The educational requirements for entrance into a medical college prior to the report were so low that it was noted that in 1880 even the ability to read and

write was not involved in determining admittance of a student into a medical school.[10]

The moral effect of the Flexner report soon was felt throughout the country and there was a marked improvement in the status of medical education within a decade following its publication. In 1904 more than half of the medical schools of the world were located in the United States; they numbered 160. By 1914, 4 years after the report, there were 102 medical schools; and in 1918 the number had dropped to 95. At present there are seventy-nine 4-year schools and six other schools with less than a 4-year program approved by the American Medical Association in the United States, including Puerto Rico, and twelve approved medical schools in Canada. A further comparison is seen in the following statistics: in 1904 only 2.5 per cent of the medical schools required any college preparation, whereas by 1918 92.2 per cent of the medical schools required at least 2 years of college. Of the 160 schools in existence in 1904, only 82 were fully approved by the inspecting teams of the Council of Medical Education. Only 6.5 per cent of all medical students were enrolled in the approved schools in 1904, yet by 1918 95.3 per cent of the students were in approved medical schools. Today all schools in operation are approved by the American Medical Association.

The American Medical Association was also instrumental in urging that holders of the medical degree have at least 1 year of internship prior to entrance into practice. It was not until 1914 that the first State—Pennsylvania—required an internship for licensure. In 1914 the American Medical Association published the first list of hospitals approved for internship; this list designated 603 hospitals as suitable for the instruction of young graduates in the clinical branches of medicine and surgery. It included 508 general hospitals offering 2,667 internships and 95 special hospitals offering training to 428 graduates. In 1958 there were 12,469 approved internships and 31,713 approved residencies in 1,265 hospitals in the United States.

Progress in residency training of doctors following an internship was accelerated in 1919, when the Council of Medical Education reported and listed the approved graduate schools. At this time there were eighteen postgraduate courses offered, only seven of which were sponsored by universities. By 1934 there were thirty-eight approved graduate schools, thirty of which were connected with a university. During 1958-1959, eighty-four medical schools offered postgraduate courses in medicine or the basic sciences.

In 1918 the American College of Surgeons appointed a committee to inspect the various hospital programs to see if they should be approved for residency training; this was continued until 1953, when a Joint Commission on Accreditation of Hospitals was formed with representatives from the American College of Surgeons, the American College of Physicians, the American Medical Association, the American Hospital Association, and the Canadian Medical Association. Recently the Canadian Medical Association has withdrawn from the Commission to inspect the programs in Canadian hospitals alone.

The history of specialization in medicine dates back to the middle of the nineteenth century, when physicians formed the various specialty societies, the first of which was the Boston Phrenological Society founded in 1832. This society disappeared in 1842. The oldest of the still-existing specialist societies in the United States is the Association of Medical Superintendents of the American Institutions for the Insane, founded in 1844, gradually evolving to become the American Psychiatric Association in 1921.

The first specialty board, the American Board of Ophthalmology, set up the requirements for adequate training in this subspecialty in 1916. This was followed by the other specialty boards, until presently there are twenty-seven examining boards which are recognized as being responsible for certification of specialists. The various boards are supervised by the Advisory Board of Medical Specialties, which was organized in 1934 to coordinate graduate education and certification of medical specialists in the United States and Canada. Each individual board has separate requirements prior to examination for certification. The names of all certified specialists are listed in the *Directory of Medical Specialists,* which is published every 2 years.

In general surgery it is necessary to have a residency of graduated responsibility of at least 4 years in an approved institution after an approved internship. The resident's last year of training must be in the capacity of a senior resident. This is the minimum requirement; some of the residency training programs are of 5 or more years in duration.

In internal medicine the requirement is 3 years of approved residency after an approved internship, together with a 2-year period of practice before the candidate is ready for examination. Time spent in military service may be applied to this 2-year waiting period.

In some of the subspecialties, such as thoracic surgery, pulmonary disease, gastroenterology, and cardiology, certification is by examination in the subspecialty only after the candidate has been certified in either general surgery or internal medicine.

World War II, with its tremendous demand for young medical officers, caused a log-jam in regard to residency training. At least ten classes graduating from approximately 1937 to 1946 contained many young doctors whose postgraduate training was interrupted by military service. Because of the tremendous demand for residencies in the period of 1946 to 1952, many additional hospitals were approved for residency training. Many of these hospitals were not connected with universities. Recently there has been a tendency to raise the standards of the individual certifying boards, as well as a more penetrating and stringent type of inspection by the Joint Commission on the Accreditation of Hospitals. Because of this, it has been necessary for many private hospitals to improve the quality of their training programs and many of them have responded by employing a full-time Director of Medical Education. This resulted in the establishment of the Association of Hospital Directors of Medical Education in 1956. Many of these hospitals are on the East Coast, but there has been a gradual expansion so that these nonuniversity-affiliated programs are now appearing in all portions of the country.

Another post-World War II development in medical education was the appearance of approved residencies in federal hospitals, including those controlled by the Army, Navy, Air Force, and Public Health Service, as well as those sponsored by the Veterans Administration. Although the military service teaching programs are designed for the training of career personnel, the need for and the value of the programs sponsored by the Public Health Service and the Veterans Administration have become increasingly apparent with the increase in hospitalization insurance plans throughout the country. These insurance plans provide that the patient has a choice of a private physician in the event of hospitalization. This has caused the gradual but progressive disappearance of the "ward," "staff," or "charity" bed in the nation's hospitals to be replaced by the semiprivate bed, which in surgery at least largely results in the loss of a teaching bed in terms of the resident carrying out the operative procedure on his own responsibility. The rate of growth of the insurance plans is shown by the following facts[7]—there has been an increase of 700 per cent in the number of Americans covered by prepaid hospitalization insurance since 1951. At the present rate of growth, it is estimated that this number will double itself every 4½ years in the future. The impact on the number of teaching beds affected is shown by a survey of an unnamed Middle Western hospital of 1,000 beds. In 1951, 99 per cent of the beds in this institution were teaching beds, while in 1957 the number had dropped to 62 per cent and was still dropping.

The federal hospitals have no private or semiprivate patients and thus all beds are teaching beds. Nearly all of the approved residencies in the Veterans Administration Hospitals are integrated with those of university hospitals, and this source of clincial teaching material will probably solve the problem of those university services which are in close proximity to a Veterans Administration Hospital with an approved residency.

However, although the Veterans Administration residency positions amount to 9 per cent of all residencies offered in this country,[6] this will obviously not solve the problem in the vast majority of the hospitals offering approved residencies. I believe that this condition will become worse in the future, and the ultimate salvation of postgraduate medical education, particularly in general surgery and its subspecialties, will require a compromise between the law, the insurance company, the patient, and the private attending surgeon. The alternative is to return to a preceptorship type of training, which in many hands can be excellent, but which has proved to be in the vast majority of cases decidedly inferior to approved institutional residency training.

SUMMARY

The evolution of medical education in the United States has been traced from the colonial era to the present. The record was very spotty until the moral impact of the Flexner report in 1910 started a revolution during the next 2 decades, with the result that American medical education, both undergraduate and postgraduate, became the best in the world. This is attested to by the large number of foreign students involved in both types of educational programs

in the United States at present. This is a mirror image of the situation which prevailed up to the 1920's, when many American students sought advanced training in the clinics of Europe.

The future of medical education has become clouded again, however, for during the past 10 years the spectre of prepaid hospitalization insurance has resulted in a progressive loss of teaching beds in the hospitals with approved residency training. The ultimate resolution of this problem is not clearly in view at the present time.

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